Navigenics Health Compass Report

For Physicians

Printed: October 20, 2010

This is not an official medical record. Physicians: Do not chart. It represents an abridged version of your patient's Navigenics results.
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<th>Page</th>
</tr>
</thead>
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<td>61</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>63</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>65</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>67</td>
</tr>
<tr>
<td>Floxacinil</td>
<td>69</td>
</tr>
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<td>Fluorouracil</td>
<td>71</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>73</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>75</td>
</tr>
<tr>
<td>Statins</td>
<td>77</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>79</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>82</td>
</tr>
<tr>
<td>Warfarin</td>
<td>84</td>
</tr>
</tbody>
</table>
About Navigenics

Navigenics, a private company based in Foster City, Calif., offers personalized, preventive pharmacogenomic and health services based on a member’s genomic risk profile. Our founders and advisors include leading genetic scientists, physicians, genetic counselors, bioethicists, patient advocates and health policy and technology experts. We are committed to grounding our service in the latest scientific knowledge about genetics, health and disease prevention, and how genes can affect drug responses, while presenting information in a highly transparent, personalized way so that our members can act on it.

How we do it

Navigenics analyzes people’s genetic makeup to give them a picture of their genetic predisposition for common, actionable conditions and medication outcomes. We look for one-letter variations in DNA (SNPs) that serve as markers of risk.

Here is a summary of the steps we take. More detail can be found at [www.navigenics.com](http://www.navigenics.com), along with extensive information explaining genetic markers and a CME course that covers such as well.

- We select genetic markers based on strong science associated with actionable conditions and medication outcomes. Our team of Ph.D. geneticists selects genetic risk markers that are significantly associated with clearly defined health conditions and medication outcomes validated by multiple well-designed studies. The studies typically have been published in top-tier journals such as Science, Nature and the New England Journal of Medicine.
- We collect DNA via a saliva sample, and then the DNA is probed for appropriate markers in a CLIA-certified lab.
- We analyze these complex results with formulae developed by our Ph.D. mathematicians and prepare a report that is easily understood, but extensively documented.

Considerations and caveats

The Navigenics Health Compass is not a diagnostic test. Our service highlights genetic predisposition to common conditions and medication outcomes, so that prevention measures may be taken, early diagnosis may be made, or appropriate medications chosen. The Navigenics Health Compass is a powerful tool. But it does have important limitations regarding certain conditions such as breast cancer, colon cancer and several others. For example, the Navigenics Health Compass addresses common genetic causes of breast cancer. It does not, however, specifically address more rare causes of familial breast cancer, such as BRCA mutations. So, individuals who have a strong family history of breast cancer, especially in relatives under age 50, may be at greater risk than the Navigenics Health Compass estimates and should consult a Genetic Counselor.


How we calculate risk

Here's how we calculate our members’ risk for the conditions and medication outcomes we cover.

- For most conditions, we start with the average lifetime risk for their gender, for people in the United States.
- Next we look at the actual risk markers we found in their genome. For most conditions, we check multiple markers.
- Then we calculate how much each marker on its own raises the risk of that condition. These “odds ratios” are based on the original scientific studies that associated these markers with disease risk.
- Finally, using a formula developed by our science team, we factor together the odds ratios for each marker, how common those markers are in the population and how common the condition is. We apply that to the average lifetime risk.
- The result is an estimate of the member’s own lifetime risk, compared with the population average.
- For some conditions, such as hemochromatosis and lactose intolerance, as well as for medication outcomes, lifetime risk estimates are not available. In these cases we indicate whether the genes analyzed indicate increased risk.
About genetic markers

More than 99 percent of our genetic code is identical from person to person. The remainder is unique among individuals. DNA, the chemical instructions that determine our genetic code, is composed of four biochemical bases that are represented by the DNA alphabet: A, T, G and C.

SNPs, or single nucleotide polymorphisms, are one-letter variations in our DNA. Each SNP (pronounced "snip") consists of two markers or variants, and each marker has two possible versions, a risk version and a non-risk version. For example, at a given SNP, the base A may be the risk marker and the base G may be the non-risk marker.

The SNPs included in the Navigenics risk estimate have been reliably shown to be associated with diseases, although it is not known exactly how they contribute to the conditions. The degree of genetic risk your patient inherits is related, in part, to how many risk markers he or she has residing at each SNP — none, one, or two. Just because your patient may have one or two risk markers does not mean that he or she will definitely develop a given health condition, but it can raise your patient's risk, especially if other lifestyle or environmental risk factors are present.

Understanding the Health Condition results table

For most conditions, each row gives your patient's estimated lifetime risk of that condition, compared with the average risk for their gender. (Note that for some conditions, such as hemochromatosis and lactose intolerance, lifetime risk estimates are not available.) Highlighted rows indicate either:

- Your patient's overall risk is greater than 25 percent or
- Your patient's risk is more than 20 percent above average for that condition or
- Your patient has increased risk for that condition.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patient's percentile</th>
<th>Patient's estimated lifetime risk</th>
<th>Average lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Condition 1</td>
<td>37%-44%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition 2</td>
<td>86%-100%</td>
<td>80%*</td>
<td>25%</td>
</tr>
<tr>
<td>Condition 3</td>
<td>37%-44%</td>
<td>4.4%</td>
<td>9%</td>
</tr>
<tr>
<td>Condition 4</td>
<td>63%-80%</td>
<td>28%*</td>
<td>35%</td>
</tr>
</tbody>
</table>

1Patient's percentile: This information allows you to see how your patient compares to other people. When compared to a reference population, your patient's SNP-based risk for the condition falls within the given range of percentiles. For Condition 1, for example, 36 percent of people have a lower genetic risk, while 45 percent have a higher genetic risk.

2Patient's lifetime risk: Your patient's risk of this condition over the course of his or her lifetime. For some conditions, such as hemochromatosis and lactose intolerance, estimated lifetime risk numbers are not available. We indicate whether the person is at increased or no increased risk for the condition.

3Average lifetime risk: The average person's risk of this condition over the course of their lifetime, depending on gender. For some conditions, such as hemochromatosis and lactose intolerance, average lifetime risk estimates are not available.

4This row is highlighted because the patient's risk is more than 20 percent above average.

5This row is highlighted because the patient's overall risk is greater than 25 percent (though lower than the average).
### Understanding the Health Condition genetic markers table(s)

<table>
<thead>
<tr>
<th>Gene or location¹</th>
<th>Risk marker²</th>
<th>Patient's markers³</th>
<th>Odds ratio⁴</th>
<th>Source⁵</th>
</tr>
</thead>
</table>

¹Gene or location: The place we looked in your patient's genome.
²Risk marker: The variant in the human genetic code that marks higher odds for this condition.
³Patient's markers: The letters we found in your patient's DNA. Any risk markers found are bold. Pending means we’re continuing to analyze your patient's DNA to provide results for this location. In most cases, we'll be able to provide results and will let you know when we get them. In a few cases, a person's DNA may not provide results at this location, even after repeat analysis. If you have questions, see our Help section or contact one of our Genetic Counselors.
⁴Odds ratio: How much a patient's odds of developing a condition are increased by his or her genotype. The higher the number, the greater the increase. An odds ratio of 1.0 corresponds to having no risk markers. (For some conditions, odds ratios are not available.)
⁵Source: A scientific journal article where the association between this location and the disease was reported.
Understanding the Medications results tables

For Medications, your patient's results are presented in two tables — one related to side effects and one related to drug effectiveness. Each row of the tables gives your patient's genetic results indicating how your patient is likely to respond to each particular pharmaceutical drug. For some medications, your patient's results indicate his/her likelihood of severe side effects. For other drugs, your patient's results indicate whether a particular medication is likely to be effective for him/her. Highlighted rows show that based on the genetic analysis, either:

- Your patient's risk of side effects is atypical (moderate or high) or
- This medication is not likely to have typical effectiveness for your patient or
- Your patient's results can help you calculate a drug dose that is more likely to be safe and effective.

**Medication Side Effects**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effect</th>
<th>Patient’s risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication 1</td>
<td>types of possible side effects (such as severe allergic reaction, nausea, etc.)</td>
<td>high risk</td>
</tr>
<tr>
<td>Medication 2</td>
<td>types of possible side effects (such as myelotoxicity, fever, etc.)</td>
<td>moderate risk</td>
</tr>
<tr>
<td>Medication 3</td>
<td>types of possible side effects (such as muscle pain, muscle damage, etc.)</td>
<td>low risk</td>
</tr>
</tbody>
</table>

1**Drug:** We analyzed this patient's genetic code to determine the person's likely risk of side effects if taking this medication.

2**Side effect:** Severe side effects that are possible with this medication because of a person's genetic markers

3**Patient's risk:** This patient's risk of severe side effects, based on the markers we found in their genetic code.

4This row is highlighted because this patient's risk of side effects is **high**, meaning that this patient's risk is greatly increased based on the markers in their genetic code.

5This row is highlighted because this patient's risk is **moderate**, meaning that this patient's risk is somewhat increased based on the markers in their genetic code.

**Medication Effectiveness**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Information</th>
<th>How effective for your patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication 1</td>
<td>reasons why this medication is used (such as to reduce risk of heart failure)</td>
<td>decreased effectiveness</td>
</tr>
<tr>
<td>Medication 2</td>
<td>reasons why this medication is used (such as to prevent blood clots, etc.)</td>
<td>may require customized dose</td>
</tr>
<tr>
<td>Medication 3</td>
<td>reasons why this medication is used (such as to lower cholesterol, etc.)</td>
<td>typical effectiveness</td>
</tr>
</tbody>
</table>

1**Drug:** We analyzed this patient's genetic code to determine how effective this medication is likely to be for them.

2**Information:** Medical conditions for which this drug is commonly used

3**How effective for your patient:** How effective this medication is for this patient, based on the markers we found in their genetic code.

4This row is highlighted because this drug's level of effectiveness for this patient is **decreased**, meaning that this person carries genetic markers that are linked to decreased levels of effectiveness.

5This row is highlighted because this drug may be safe and effective after this person's **dose is customized**, meaning that these genetic markers can be used to help find a dose tailored to the patient's genetic makeup.
Understanding the Medications genetic markers tables

For your patient's Medications results, the genetic markers tables differ from those that appear in the patient's Health Conditions results. These differences reflect the distinct ways that your patient's Medications results are discussed. Below, you'll find a detailed explanation of your patient's Medications genetic markers tables.

<table>
<thead>
<tr>
<th>Gene or location¹</th>
<th>Test SNP²</th>
<th>Patient's markers³</th>
<th>Scientific name⁴</th>
<th>What it means⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA1</td>
<td>rs112233</td>
<td>GG</td>
<td>*2/*3</td>
<td>high risk</td>
</tr>
<tr>
<td>BBB2</td>
<td>rs445566</td>
<td>CT</td>
<td>*1/*3C</td>
<td>moderate risk</td>
</tr>
<tr>
<td>CCC3</td>
<td>rs778899</td>
<td>AA</td>
<td>*1/*1</td>
<td>low risk</td>
</tr>
</tbody>
</table>

¹Gene or location: The place we looked in your patient's genome. Some SNPs are in or near a gene while others are not. These are denoted by their location in the genome.
²Test SNP: The actual SNP analyzed in this test. "rs" refers to “reference sequence,” the location in the genome as identified by researchers.
³Patient's markers: What we found in your patient's genome based on the SNP(s) we tested.
⁴Scientific name: The technical description of your patient's genotype. An asterisk is pronounced “star”, a term used to refer to pharmacogenomic genotypes.
⁵What it means: What your patient's genetic results mean in terms of potential response to this medication.
**Cover Page for Personal Results - Navigenics Health Compass**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique Barcode Identifier</td>
<td>037-10322763122</td>
</tr>
<tr>
<td>Laboratory Barcode</td>
<td>00013156</td>
</tr>
<tr>
<td>Sample Type</td>
<td>Saliva</td>
</tr>
<tr>
<td>Sample Collection Date</td>
<td>March 31, 2010</td>
</tr>
<tr>
<td>Date Received at Laboratory</td>
<td>May 06, 2010</td>
</tr>
<tr>
<td>Sample received to have met acceptable criteria for testing?</td>
<td>Yes</td>
</tr>
<tr>
<td>Sample forwarded to another laboratory for testing?</td>
<td>No</td>
</tr>
<tr>
<td>Date Report is Generated</td>
<td>July 15, 2010</td>
</tr>
</tbody>
</table>

Navigenics Laboratory
910 Riverside Parkway, Suite 60
West Sacramento, CA 95605
Douglas S. Harrington, MD — Laboratory Director
Your patient's Health Condition results

For most conditions, each row gives your patient's estimated lifetime risk of that condition (where available), compared with the average risk for his or her gender. Highlighted rows indicate either:

- Your patient's overall risk is greater than 25 percent
- Your patient's risk is more than 20 percent above average for that condition or
- Your patient has increased risk for that condition.

We calculate the estimated lifetime risk for your patient as noted in the "How we calculate risk" section on page 4.

We present this value and the population average. It is important to note that an elevated risk (orange highlight) is assigned for one of the three reasons noted here. Also note that unhighlighted rows may underestimate risk in certain cases, as noted in our results for certain conditions. It is important to review the entire Assessing Risk section on our website, at http://www.navigenics.com/visitor/forphysicians/tools/assessingrisk.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patient's percentile</th>
<th>Patient's estimated lifetime risk</th>
<th>Average lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal aneurysm</td>
<td>23% - 77%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>0% - 76%</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>57% - 75%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Brain aneurysm</td>
<td>23% - 77%</td>
<td>0.91%</td>
<td>0.90%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>83% - 85%</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>60% - 62%</td>
<td>0.06%</td>
<td>0.11%</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>30% - 33%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>64% - 66%</td>
<td>0.52%</td>
<td>0.54%</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>49% - 82%</td>
<td>3.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Diabetes, type 2</td>
<td>29% - 31%</td>
<td>23%</td>
<td>30%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0% - 44%</td>
<td>0.47%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>34% - 39%</td>
<td>1.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Heart attack</td>
<td>46% - 73%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Hemochromatosis, HFE-related</td>
<td>0% - 57%</td>
<td>extremely low risk / no risk markers present (non-carrier)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>0% - 95%</td>
<td>low risk</td>
<td>N/A</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>79% - 100%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Lupus</td>
<td>47% - 49%</td>
<td>0.19%</td>
<td>0.26%</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>59% - 61%</td>
<td>2.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0% - 61%</td>
<td>1.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>22% - 39%</td>
<td>0.36%</td>
<td>0.77%</td>
</tr>
<tr>
<td>Obesity</td>
<td>55% - 85%</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>44% - 61%</td>
<td>47%</td>
<td>47%</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2% - 4%</td>
<td>1.8%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>5% - 12%</td>
<td>1.5%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>98% - 100%</td>
<td>12%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0% - 23%</td>
<td>0.55%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Stomach cancer, diffuse</td>
<td>0% - 13%</td>
<td>0.45%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
1 **Patient's percentile**: When compared to a sample population, your patient's SNP-based risk for the condition falls within the given range of percentiles.

2 **Patient's estimated lifetime risk**: Your patient's risk of this condition over the course of their lifetime. For some conditions, such as hemochromatosis and lactose intolerance, estimated lifetime risk numbers are not available. In these cases, we indicate whether the person is at increased or no increased risk for the condition.

3 **Average lifetime risk**: The average person's risk of this condition over the course of their lifetime, depending on gender. For some conditions, such as hemochromatosis and lactose intolerance, average lifetime risk estimates are not available.
Your patient's Medications results

For Medications, your patient's results are presented in two tables — one for side effects and one for drug effectiveness. Each row of the tables gives your patient's genetic result indicating how your patient is likely to respond to that particular drug. For some medications, your patient's results indicate his/her genetic likelihood of severe side effects. For others, your patient's results indicate whether a particular medication is likely to be effective for him/her.

Highlighted rows indicate that based on this genetic analysis, either:

- Your patient's risk of side effects is atypical (moderate or high) or
- This medication is not likely to have typical effectiveness for your patient or
- You can use these genetic results to help find a dose of this drug that is more likely to be safe and effective for your patient.

It is important to note that an atypical result (orange or dark highlight) is assigned for one of these three reasons. Also note that low risk or typical results (unhighlighted rows) also provide valuable information on drug safety and efficacy that can help guide personalized medication choices.

It's also important to note that these results may occasionally overestimate or underestimate risk in certain cases, as noted in our results for certain conditions. For this reason, we strongly encourage you to review your patient's results for each condition carefully.

Medication Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effect</th>
<th>Patient’s risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (Ziagen®)</td>
<td>Severe allergic reaction, including fever, rash, and nausea</td>
<td>low risk</td>
</tr>
<tr>
<td>Carbamazepine (Carbatrol®)</td>
<td>Life-threatening dermatological syndromes that include fever, rash, and peeling skin.</td>
<td>unable to be determined</td>
</tr>
<tr>
<td>Floxacinil (Floxapen®)</td>
<td>Severe liver toxicity, leading to liver damage</td>
<td>low risk</td>
</tr>
<tr>
<td>Fluorouracil (Efudex®)</td>
<td>Severe, potentially fatal toxicity</td>
<td>low risk</td>
</tr>
<tr>
<td>Irinotecan (Camptosar®)</td>
<td>Severe reactions, including suppression of the immune system</td>
<td>moderate risk</td>
</tr>
<tr>
<td>Simvastatin (Vytorin®, Zocor®)</td>
<td>Muscle pain and damage</td>
<td>low risk</td>
</tr>
<tr>
<td>Thiopurines (Azasan®)</td>
<td>Severe bone marrow complications</td>
<td>low risk</td>
</tr>
<tr>
<td>Succinylcholine (Anectine®)</td>
<td>Prolonged, potentially dangerous paralysis of the breathing muscles</td>
<td>low risk</td>
</tr>
</tbody>
</table>

1Drug: We analyzed your patient's genetic code to determine your patient's genetic risk of side effects if taking this drug.
2Side effects: Severe side effects associated with this medication
3Patient’s risk: Your patient’s risk of side effects, based on the markers we found in your patient’s genetic code.
## Medication Effectiveness

<table>
<thead>
<tr>
<th>Drug</th>
<th>Information</th>
<th>How effective for your patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers (Coreg®, many others)</td>
<td>Used to treat and prevent cardiovascular disease</td>
<td>typical effectiveness</td>
</tr>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>Used to prevent blood clots and conditions linked to them, such as heart attack and stroke</td>
<td>typical effectiveness</td>
</tr>
<tr>
<td>Statins (Pravachol®, Zocor®, many others)</td>
<td>Used to treat high cholesterol and help prevent heart disease</td>
<td>typical effectiveness</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>Used to treat and prevent blood clots and heart-related conditions, such as atrial fibrillation and heart attack</td>
<td>likely to require customized dose</td>
</tr>
</tbody>
</table>

1**Drug:** We analyzed your patient's genetic code to determine how effective this medication is for him/her.

2**Information:** Medical conditions for which this drug is commonly used

3**How effective for your patient:** How effective this medication is for your patient, based on the markers we found in your patient's genetic code
Abdominal aneurysm

Your patient's estimated lifetime risk: **1.5% (15 per 1,000)**
Average lifetime risk: **1.5% (15 per 1,000)**

Your patient has 1 of the 2 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21</td>
<td>G</td>
<td>A G</td>
<td>1.36</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at one place on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of abdominal aneurysm. At this location, there are two markers, for a total of two possible risk markers. The table above shows your patient's markers. Your patient has one of the two risk markers we looked for.

The genetics of abdominal aneurysm

An abdominal aneurysm usually results from a mix of genetic and environmental causes. Family and case-control studies indicate that about 72 percent of your patient's potential risk is caused by genetic factors.

Men are four times more likely than women to develop this type of aneurysm, with men who have a history of smoking and those over 65 at the highest risk.

For younger individuals, having smoked or having a family history increase risk.

A marker found on Chromosome 9 in the region known as p21.3, associated with heart disease in other studies, can also raise the likelihood of an abdominal aneurysm.

Your patient's genetic risk, in the context of his or her family history and other risk factors, can signal whether your patient would benefit from screening for an aneurysm.

Further reading

Prevention

Dalman, R.L. Annals of the New York Academy of Sciences, vol. 1085, p. 92, November 2006. "AAA disease: mechanism, stratification, and treatment." No medical therapy has proven effective in preventing small abdominal aneurysms from growing larger prior to surgical repair. Armed with new tools such as MRI to image blood flow, researchers are investigating interventions such as supervised exercise to prevent the progression of small aneurysms. This study was the precursor for Stanford University's current clinical trial of supervised exercise to slow the rate of aneurysm growth.

Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Alzheimer's disease

Your patient's estimated lifetime risk: **10% (10 per 100)**
Average lifetime risk: **17% (17 per 100)**

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
</table>

see page 6 for an explanation of this table format

Condition alert
Navigenics tests for markers associated with the common, or late-onset, form of Alzheimer's, which generally develops after age 65. There is also a very rare early form with a strong hereditary component, which Navigenics does not test for. If any of your patient's relatives have been diagnosed with Alzheimer's disease before age 60, your patient should consult with a Genetic Counselor.

Your patient's genetic results

On your patient's genome, we looked at one place in your patient's APOE gene where two one-letter differences in the genetic code can combine to raise your patient's odds of Alzheimer's disease. At this location, three possible markers, called E2, E3, and E4, are determined by the two one-letter differences in the APOE gene. A person might have zero, one, or two copies of the risk marker, E4. The table above shows your patient's markers.

The genetics of Alzheimer's disease

Alzheimer's disease is believed to be caused by a mix of genetic and environmental factors, with inherited factors accounting for about 62 percent of the risk, according to studies of twins. Many other non-genetic risk factors have been proposed, but only advanced age and family history are verified. The common, or late-onset, form of Alzheimer's generally begins after age 65.

Early-onset Alzheimer's disease, which begins before age 60, is even more strongly genetic in its cause, but very rare — it represents less than 2 percent of cases. Navigenics does not test for this rare kind of Alzheimer's disease. If you have family members who developed the disease at an early age, you should consult a Genetic Counselor.

More than 1,000 scientific papers have reported associations between various genetic markers and late-onset Alzheimer's disease, but most of these studies do not meet Navigenics' rigorous standards. However, there is a strong and well-established association between the disease and a gene called APOE. APOE comes in three different versions: APOE-2, APOE-3 and APOE-4. Having one or more copies of APOE-4 raises your chances of getting Alzheimer's disease. Additional genetic factors that contribute to Alzheimer's will undoubtedly be validated in the future, but APOE is currently, and is likely to continue to be, the single most important genetic factor related to late-onset Alzheimer's.

In several published studies, more than half of the subjects with late-onset Alzheimer's had at least one copy of APOE-4. But having the APOE-4 variant does not necessarily mean that you will develop the disease. About 3 percent of the Caucasian population has two copies of APOE-4, but not all of them develop Alzheimer's.
Further reading

Prevention

Agency for Healthcare Research and Quality Evidence Review No. 114. "Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases."


The National Institute on Aging's publication "Can Alzheimer's Disease Be Prevented?" summarizes the most current research avenues.


Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Atrial fibrillation

Your patient's estimated lifetime risk: **25% (25 per 100)**
Average lifetime risk: **23% (23 per 100)**

Your patient has 1 of the 4 risk markers we looked for.

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see page 6 for an explanation of this table format

Your patient's genetic results

We looked at two places on your patient's genome where a one-letter difference in the genetic code raises your patient's odds of atrial fibrillation. At each location, there are two markers, for a total of four possible risk markers. The table above shows your patient's markers. Your patient has one of the four risk markers we looked for.

The genetics of atrial fibrillation

Atrial fibrillation becomes increasingly common with age and generally results from a mix of genetic and noninherited risk factors. To assess increased genetic risk, we are testing several markers for a particular location on the genome adjacent to PITX2, a gene involved in heart development.

Further reading

Prevention


Frost, L. et al. American Journal of Medicine, vol. 118, p. 489, May 2005. "Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer and Health Study." Researchers analyzing the 47,589 participants in a huge prospective Danish public health study concluded that being overweight or obese is associated with a greater chance of a diagnosis of atrial fibrillation or flutter.


Mazaffarian, D. et al. Circulation, vol. 110, p. 368, July 27, 2004. "Fish intake and risk of incident atrial fibrillation." Researchers conducted a prospective study of 4,815 healthy people aged 65 and older. They observed that eating tuna or other baked or broiled fish one to four times a week gave a 28 percent lower risk of atrial fibrillation, and five or more fish meals a week conferred 31 percent less risk, compared to eating these fish once a month or not at all. Researchers speculate that omega-3 fatty acids from fish may have antiarrhythmic effects on atrial muscle. Fast-food fans, take note: Fried fish and fish sandwiches made from varieties low in omega-3 fatty acids raised risk.
Mukamal, K. et al. Circulation, vol. 112, p. 1736, Sept. 20, 2005. "Alcohol consumption and risk of atrial fibrillation in men and women. The Copenhagen City Heart Study." This study found that heavy drinking (defined as more than 35 drinks per week) raises risk for atrial fibrillation.


Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Brain aneurysm

Your patient's estimated lifetime risk: **0.91% (91 per 10,000)**
Average lifetime risk: **0.90% (90 per 10,000)**

Your patient has 1 of the 2 risk markers we looked for.

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see page 6 for an explanation of this table format

Your patient's genetic results

We looked at one place on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of a brain aneurysm. At this location, there are two markers, for a total of two possible risk markers. The table above shows your patient's markers. Your patient has one of the two risk markers we looked for.

The genetics of brain aneurysm

Scientists have found that African-Americans are twice as likely to develop a brain aneurysm as whites. Women are also twice as likely to develop a brain aneurysm or to suffer a ruptured aneurysm as men. Other studies have shown that brain aneurysms sometimes run in families. Among first-degree relatives of patients with a ruptured aneurysm, such as parents and siblings, the risk of a ruptured brain aneurysm is four times higher than the risk in the general population. Familial aneurysms also tend to rupture at a smaller size and when patients are younger. Siblings may experience rupture in the same decade of life.

Further reading

Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Breast cancer

Your patient's estimated lifetime risk: **17% (17 per 100)**
Average lifetime risk: **13% (13 per 100)**

Your patient has **9** of the **14** risk markers we looked for.

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see page 6 for an explanation of this table format

Condition alert

Navigenics tests for common markers associated with breast cancer. Much less common are single-gene mutations that can lead to breast cancer, which Navigenics does not test for.

You've probably heard about BRCA, the first gene linked to breast and ovarian cancer. Navigenics does not test for the BRCA variants, which account for less than 10 percent of all breast cancer cases. People with a family history of breast cancer, especially in a close relative such as a parent or sibling, should consider consulting a Genetic Counselor.

At Navigenics, we focus on the 90 percent of breast cancer cases that are not caused by such rare variants. We look for genetic markers that are common in the U.S. population.

If your patient answers "yes" to any of these questions, your patient should consult a Genetic Counselor for consideration of further testing:

- Have you or anyone in your family had breast cancer before age 50, cancer in both breasts at any age or ovarian cancer at any age?
- Have two or more close relatives on the same side of your family (maternal or paternal) had breast or ovarian cancer, or has one relative had both?
- Do you have any male relatives with breast cancer?
- Do you have Ashkenazi (Eastern European) Jewish ancestry and at least one family member with breast or ovarian cancer at any age?
- Do you have any relatives with an identified genetic mutation that increases their risk for cancer?
Your patient's genetic results

We looked at seven places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of breast cancer. At each location, there are two markers, for a total of 14 possible risk markers. The table on the previous page shows your patient's markers. Your patient has nine of the 14 risk markers we looked for.

The genetics of breast cancer

Most of the risk of breast cancer comes from a combination of lifestyle and environmental factors, but studies show that about 27 percent of the risk for breast cancer is genetic. A good part of this inherited risk appears to result from combinations of common genes, each with a modest effect. This means that many people have these genes, but the increased risk associated with each gene is relatively small.

Knowing your patient inherited risk factors can help guide lifestyle habits. Depending on your patient's genetic makeup, she may respond better or worse than others to certain drugs and treatments. As knowledge about genetic risk factors advances, it can illuminate ways to tailor more effective prevention and treatment strategies.

Further reading

Prevention

Key, Timothy et al. Journal of the National Cancer Institute, vol. 95, p. 1218, August 2003. "Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women." This paper confirms the link between excess body weight and increased risk of breast cancer.


Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Celiac disease

Your patient's estimated lifetime risk: **0.06% (6 per 10,000)**
Average lifetime risk: **0.11% (11 per 10,000)**

Your patient has **9** of the **20** risk markers we looked for.

<table>
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<th>Gene or location</th>
<th>Risk marker</th>
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<td>Nature Genetics, 2008</td>
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</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at 10 places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of celiac disease. At each location, there are two markers, for a total of 20 possible risk markers. The table above shows your patient's markers. Your patient has nine of the 20 risk markers we looked for.

The genetics of celiac disease

Celiac disease is associated with certain HLA (human leukocyte antigen) genes involved in provoking the immune response and inflammation. About 90 percent of patients diagnosed with celiac disease carry a set of genetic markers called HLA-DQ2. (Most of the rest have another set called HLA-DQ8.) But having HLA-DQ2 does not mean that your patient definitely will get celiac disease.

Further reading

Genetics


Van Heel, D.A. et al. Nature Genetics, published online June 10, 2007. "A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21." This study found that people who have celiac disease are more likely than others to be lacking a particular DNA sequence; the sequence influences two proteins, interleukin2 and interleukin-21, which protect against inflammation.
More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Colon cancer

Your patient's estimated lifetime risk: **5% (50 per 1,000)**
Average lifetime risk: **5% (50 per 1,000)**

Your patient has **2** of the **10** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
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<th>Source</th>
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</table>

Condition alert

Navigenics tests for common markers associated with colon cancer. Much less common are single-gene mutations that can lead to colon cancer, which Navigenics does not test for. If your patient answers "yes" to any of these questions, your patient should consult a Genetic Counselor for consideration of further testing:

- Have you or anyone in your family had colon cancer before the age of 50, or multiple colon polyps?
- Have two or more close relatives on the same side of your family (maternal or paternal) had colon, uterine or ovarian cancer, or has one relative had more than one of these cancers?
- Do you have Ashkenazi (Eastern European) Jewish ancestry and at least one family member with colon cancer at any age?
- Do you have any relatives with an identified genetic mutation that increases their risk for cancer?

Your patient's genetic results

We looked at five places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of colon cancer. At each location, there are two markers, for a total of 10 possible risk markers. The table above shows your patient's markers. Your patient has two of the 10 risk markers we looked for.

The genetics of colon cancer

We test for common variants that meet our standards for having an established association with colon cancer. We do not test for rare hereditary colon cancer syndromes, such as those caused by mutations in single genes.

Further reading

Prevention


This paper reports on one of the largest ongoing studies of lifestyle factors affecting cancer risk. In this study the authors found that participants who were most active had a significantly lower risk of colon cancer than their more sedentary counterparts.

Ingraham, B.A. et al. Current Medical Research and Opinion, vol 24, p. 139. January 2008. "Molecular basis of the potential of vitamin D to prevent cancer." This article reviews research from several scientific disciplines and concludes that there is increasing evidence to support the hypothesis that vitamin D can protect against cancer.

Martinez, M.E. Recent Results in Cancer Research, vol. 166, p. 177, 2005. "Primary prevention of colorectal cancer: Lifestyle, nutrition, exercise." This article provides an overview of many of the lifestyle factors thought to contribute to colon cancer and concludes there is sufficient evidence that it is possible to prevent the disease by following a healthy lifestyle.


Genetics


Tomlinson, Ian et al. Nature Genetics, vol. 40, p. 623, May 2008. "A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3." In this study, researchers found two previously unreported locations on the genome linked with a higher risk of colorectal cancer.


More information

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Crohn's disease

Your patient's estimated lifetime risk: **0.52% (52 per 10,000)**
Average lifetime risk: **0.54% (54 per 10,000)**

Your patient has **23** of the **54** risk markers we looked for.

<table>
<thead>
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<td>G</td>
<td>A G</td>
<td>1.13</td>
<td>Nature Genetics, 2008</td>
</tr>
<tr>
<td>ORMDL3</td>
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<td>A G</td>
<td>1.12</td>
<td>Nature Genetics, 2008</td>
</tr>
<tr>
<td>8q24</td>
<td>A</td>
<td>A G</td>
<td>1.08</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>
Your patient's genetic results

We looked at 27 places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of Crohn's disease. At each location, there are two markers, for a total of 54 possible risk markers. The table on the previous page shows your patient's markers. Your patient has 23 of the 54 risk markers we looked for.

For most markers, we look to see if one of two specific letters is present at a specific place in the genetic code. For example, your patient may have an "A," which is associated with an increased odds of Crohn's, instead of a "T," which doesn't confer a risk.

However, one of the markers for Crohn's disease, the NOD2 (CARD15)-1007fs marker, works a little differently. For this marker we look to see if there is an extra letter in the genetic code, specifically a "C," also known as an insertion. Having this extra "C" increases the odds of having Crohn's, while having no extra "C" does not.

The genetics of Crohn's disease

Crohn's disease is a form of chronic inflammatory bowel disease that results from the complex interactions of genetic and non-inherited risk factors. Siblings of individuals with Crohn's disease are at 30 to 40 times higher risk than the general population for developing the condition. People of European descent have the highest risk of this condition, and those with Ashkenazi (Eastern European) Jewish heritage have a four to five times greater chance of developing Crohn's disease than the general population.

Exactly how Crohn's disease develops is not well understood. It seems that the condition may be triggered by an abnormal immune response to environmental stress such as a bacterial infection in the digestive tract.

Crohn's disease is difficult to diagnose because of the myriad of at times vague and variable symptoms. Knowing whether your patient has an increased chance of developing Crohn's disease based on his or her genetic inheritance can help you take measures to detect the disease early and treat it promptly.

Further reading

Genetics


Duerr, R.H. et al. Science, vol. 314, p. 1461, Dec. 1, 2006. "A genome-wide association study identifies IL23R as an inflammatory bowel disease gene." This study found that the IL23R gene, a gene that has long been known to play a role in inflammatory processes, is associated with Crohn's disease.

Parkes, M. et al. Nature Genetics, published online June 6, 2007. "Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility." This study found four additional genetic associations with Crohn's disease.

Wellcome Trust Case Control Consortium, Nature, vol. 447, p. 661, June 7, 2007. "Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls." This large study replicated previously discovered genetic associations with Crohn's disease and found four new ones.

More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Deep vein thrombosis

Your patient's estimated lifetime risk: **3.3% (33 per 1,000)**
Average lifetime risk: **3.6% (36 per 1,000)**

Your patient has **2** of the **8** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
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<tr>
<td>F5-Leiden</td>
<td>T</td>
<td>C C</td>
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<td>Journal of the American Medical Association, 2008</td>
</tr>
<tr>
<td>F2-G20210A</td>
<td>A</td>
<td>G G</td>
<td>1.0</td>
<td>Journal of the American Medical Association, 2008</td>
</tr>
<tr>
<td>SERPINC1</td>
<td>T</td>
<td>C C</td>
<td>1.0</td>
<td>Journal of the American Medical Association, 2008</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Condition alert

An increased likelihood of having a deep vein thrombosis (DVT) can be inherited or acquired. The most common inherited causes are factor V Leiden and the prothrombin G20210A mutation, which are included in the Navigenics test. Additional confirmation of a positive test, however, is always appropriate.

Another common risk factor for DVT is having elevated levels of homocysteine in the blood; this can be either inherited or acquired. There are also other genetic risk factors for DVT, including Protein C, Protein S, and antithrombin deficiencies. Navigenics does not currently offer testing for these rare factors, which are generally measured by testing the actual levels of these substances in the body, rather than by a genetic test.

Regardless of your patient's Navigenics test results, if the patient has a personal or family history of DVT, especially in someone under age 50; if the same relative had more than one clot; or if there is a family history of recurrent pregnancy loss (e.g., the same person has had more than three pregnancy losses), there may be an underlying genetic cause not covered by the Navigenics panel. If any of these circumstances apply in your patient's family, it's a good idea to discuss whether additional testing may be appropriate.

Your patient's genetic results

We looked at four places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of DVT. At each location, there are two markers, for a total of eight possible risk markers. The table above shows your patient's markers. Your patient has two of the eight risk markers we looked for.
The genetics of deep vein thrombosis

Deep vein thrombosis (DVT) is a blood clot that forms in the deep veins, usually in the legs or pelvis. Sometimes, blood clots that form in the deep veins move to the lungs and get stuck there. This is called a pulmonary embolism. Together, these two conditions are known as venous thromboembolisms (VTE). More than 60,000 Americans die each year from venous thromboembolisms.

Several genetic factors have been identified that increase risk for deep vein thrombosis and pulmonary emboli. The two most common genetic variants are Factor V Leiden and the Factor II (Prothrombin) mutation. Factor V Leiden is resistant to a protein known as activated protein C, which helps limit clotting. The exact mechanism by which the Factor II (Prothrombin) mutation promotes clotting is less clear. Both of these variants are common in whites but extremely rare in Asians and Africans. Other genetic variants that increase risk for thrombosis exist, but these are less common and are not included in the Navigenics service. (See the "Condition Alert" on this page.)

Further reading

Prevention

Baccarelli, Andrea et al. Archives of Internal Medicine, vol. 168, p. 920, May 12, 2008. "Exposure to particulate air pollution and risk of deep vein thrombosis." Breathing microscopic particles can raise the risk of heart attack and stroke. In this study, Italian researchers found that such particles also increase DVT risk.


Glynn, R.J. et al. Annals of Internal Medicine, vol. 147, p. 525, October 16, 2007. "Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial." This study suggests that long-term, low-dose aspirin treatment has little effect on preventing DVT in initially healthy women, but short-term aspirin therapy can lower the chances of DVT in high-risk patients.


Pomp, E.R. et al. American Journal of Hematology, vol. 83, p. 97, February 2008. "Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use." This study involved nearly 4,000 people who had had an episode of DVT and nearly 5,000 who had not. Researchers found that women who smoked and used oral contraceptives had more than eight times the DVT risk of nonsmoking women who didn't use oral contraceptives.

Steffen, L.M. et al. Circulation: Journal of the American Heart Association, vol. 115, p. 188, 2007. "Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology." This study of African-American and Caucasian middle-aged adults showed that eating four or more servings of fruit and vegetables daily or at least one serving of fish per week is linked to fewer cases of DVT.
Vandenbroucke, J.P. et al. New England Journal of Medicine, vol. 344, p. 1527. "Oral contraceptives and the risk of venous thrombosis." This article reviews the research on birth control pills and deep vein thrombosis and concludes that taking the pills does raise risk.


**Genetics**

Bezemer, I. et al. JAMA vol. 299, p. 1306, 2008. "Gene variants associated with deep vein thrombosis." Two common genetic variants, factor V Leiden (FVL) and prothrombin G20210A, have been consistently associated with deep vein thrombosis but still only explain a fraction of the clots that occur. Researchers studied 443 people with DVT and 453 healthy controls from the Leiden Thrombophilia Study. They reproduced the promising gene variants in three subsequent studies to identify variants associated with DVT, including the region around the variant in CYP4V2 associated with both DVT and factor XI levels and the SERPINC1 gene, located near genes involved in blood coagulation. Variants in the GP6 gene, which plays a role in the aggregation of blood cells, also looked promising but may have been a false result of statistical chance.

Emmerich, J. et al. Thrombosis and Haemostasis, vol. 86, p. 809, 2001. "Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism &mdash; pooled analysis of 8 case-control studies including 2310 cases and 3204 controls." Researchers pooled eight studies to estimate the risk of clots in the deep veins of patients with risk variants for the factor V Leiden and prothrombin factor II G20210A mutations. They concluded that the combination of these risk variants raised chances for clots. Researchers also found that women who carried one of these variants and took oral contraceptives had a significantly higher risk of clotting.

**More information**

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Diabetes, type 2

Your patient's estimated lifetime risk: **23% (23 per 100)**
Average lifetime risk: **30% (30 per 100)**

Your patient has **17** of the **36** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
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<tbody>
<tr>
<td>chr11.41871942</td>
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<td>TCF7L2</td>
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<td>LOC441171</td>
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<td>KCNQ1</td>
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<td>PPARG</td>
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<td>Science, 2007</td>
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<td>CDKAL1</td>
<td>G</td>
<td>A A</td>
<td>1.0</td>
<td>Nature Genetics, 2007</td>
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<tr>
<td>FTO</td>
<td>A</td>
<td>A C</td>
<td>1.16</td>
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<td>CDKN2A/B</td>
<td>T</td>
<td>T T</td>
<td>1.39</td>
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<tr>
<td>SLC30A8</td>
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<td>C C</td>
<td>1.39</td>
<td>Science, 2007</td>
</tr>
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<td>NOTCH2</td>
<td>T</td>
<td>G T</td>
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<td>KCNJ11</td>
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<td>G G</td>
<td>1.0</td>
<td>Science, 2007</td>
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<td>JAZF1</td>
<td>T</td>
<td>C T</td>
<td>1.1</td>
<td>Nature Genetics, 2008</td>
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<td>HHEX</td>
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<td>C T</td>
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<td>17q12-TCF2</td>
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<td>TSPAN8</td>
<td>C</td>
<td>T T</td>
<td>1.0</td>
<td>Nature Genetics, 2008</td>
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</tbody>
</table>

Your patient's genetic results

We looked at 18 places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of type 2 diabetes. At each location, there are two markers, for a total of 36 possible risk markers. The table above shows your patient's markers. Your patient has 17 of the 36 risk markers we looked for.

The genetics of type 2 diabetes

Type 2 diabetes is a common condition that results from complex interactions of genetic and non-inherited risk factors. Environment and lifestyle, and diet and exercise in particular, on average are responsible for about one-third of the risk of developing type 2 diabetes.
Further reading

Prevention


O'Keefe, J.H. et al. Journal of the American College of Cardiology, vol. 22, p. 249, January 2008. "Dietary strategies for improving post-prandial glucose, lipids, inflammation and cardiovascular health." These researchers summarized findings that a diet high in minimally processed, high-fiber foods such as vegetables, fruits, whole grains, legumes and nuts reduces the after-meal increase in glucose, triglycerides and inflammation.

Sigal, R. et al. Diabetes Care, vol. 27, p. 2518, October 2004. "Physical activity/exercise and type 2 diabetes." This review of the past 10 years of studies sponsored by the American Diabetes Association showed that a structured program of aerobic exercise and resistance training is even more effective for preventing and treating diabetes than drugs.

Zhang, C. et al. Circulation, vol. 117, p. 1658, 2008. "Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women." In a study of more than 44,000 women, researchers found that women with waists greater than 35 inches were 79 percent more likely to die prematurely from diabetes and cardiovascular problems than those with waists smaller than 27 inches.

Genetics

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT et al., Science, vol. 316, p. 1331; published online April 26, 2007. "Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels." This study, in conjunction with two others published at the same time, identified new risk markers for type 2 diabetes and confirmed some already found.

Florez, J.C. et al. New England Journal of Medicine, vol. 355, p. 241, July 20, 2006. "TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program." This study followed up on the people who took part in the Diabetes Prevention Program, confirming that a significant percentage of them did have a risk marker (which was discovered after the program was conducted).

Grant, Struan F. et al. Nature Genetics, vol. 38, p. 320, March 2006. "Variant of Transcription Factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes." This study found an association between a genetic variant and type 2 diabetes.

Scott, Laura J. et al. Science, vol. 316, p. 1341; published online April 25, 2007. "A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants." This study found more genetic variants associated with type 2 diabetes and confirmed some that were already known.


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results. If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Glaucoma

Your patient's estimated lifetime risk: **0.47% (47 per 10,000)**
Average lifetime risk: **2.4% (240 per 10,000)**

Your patient has **0** of the **2** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
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<tbody>
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<td>C C</td>
<td>1.0</td>
<td>Science, 2007</td>
</tr>
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</table>

Your patient's genetic results

We looked at one place on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of exfoliation glaucoma. At each location, there are two markers, for a total of two possible risk markers. The table above shows your patient's markers. Your patient has zero of the two risk markers we looked for.

The genetics of glaucoma

Glaucoma is a common disease of aging. We test for a genetic marker associated with exfoliation glaucoma, a subtype of open-angle glaucoma, which is the most common type of glaucoma. Knowing whether your patient has a genetic susceptibility to glaucoma can help with early detection of this disease.

Further reading

Prevention


Heijl, A. et al. Archives of Ophthalmology, vol. 120, p. 1268, October 2002. "Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial." This study compared newly diagnosed glaucoma patients who were treated for elevated eye pressure with those who went without treatment. It found that treating eye pressure slowed progression of the disease.


Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Graves' disease

Your patient's estimated lifetime risk: **1.7% (17 per 1,000)**
Average lifetime risk: **2.3% (23 per 1,000)**

Your patient has **1** of the **6** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
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</thead>
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<tr>
<td>DRB1*0301</td>
<td>T</td>
<td>C C</td>
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<td>American Journal of Human Genetics, 2005</td>
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<td>PTPN22</td>
<td>A</td>
<td>A G</td>
<td>1.66</td>
<td>Rheumatology, 2007</td>
</tr>
</tbody>
</table>

*see page 6 for an explanation of this table format*

Your patient's genetic results

We looked at three places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of Graves' disease. At each location, there are two markers, for a total of six possible risk markers. The table above shows your patient's markers. Your patient has one of the six risk markers we looked for.

The genetics of Graves' disease

Graves' disease is the most common type of hyperthyroidism (overactive thyroid). About two-thirds of the risk for Graves' disease is inherited. The condition is more common in women than in men.

Further reading

Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Heart attack

Your patient's estimated lifetime risk: **26% (26 per 100)**
Average lifetime risk: **25% (25 per 100)**

Your patient has 2 of the 4 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21</td>
<td>G</td>
<td>A G</td>
<td>1.28</td>
<td>Science, 2007</td>
</tr>
<tr>
<td>MTHFD1L</td>
<td>A</td>
<td>A G</td>
<td>1.23</td>
<td>New England Journal of Medicine, 2007</td>
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</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at two places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of heart attack. At each location, there are two markers, for a total of four possible risk markers. The table above shows your patient's markers. Your patient has two of the four risk markers we looked for.

The genetics of heart attack

Heart disease is caused by the interaction of multiple genetic and environmental factors. There are several ways DNA may increase heart attack risk. Some genetic variations can make your patient more vulnerable to established risk factors, such as high cholesterol.

Other genes may increase your patient's risk of stroke, peripheral artery disease and Type 2 diabetes, contributing to heart disease. Currently identified genes do not account for all of the risk connected with a family history of heart disease, so more genes remain to be identified.

Further reading

Prevention


Genetics


Samani, N. New England Journal of Medicine, vol. 357, p. 443, August 2, 2007. “A common variant on chromosome 9p21 affects the risk of myocardial infarction.” This paper confirmed the 9p21 variant as a risk factor for heart attack and also identified another risk variant, MTHFD1L.

More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Hemochromatosis, HFE-related

Your patient's risk of iron overload: extremely low risk
Your patient's HFE gene status: no risk markers present (non-carrier)

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE-C282Y</td>
<td>A</td>
<td>G G</td>
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<td>Genetics in Medicine, 2000</td>
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<td>HFE-H63D</td>
<td>G</td>
<td>C C</td>
<td>N/A</td>
<td>Genetics in Medicine, 2000</td>
</tr>
<tr>
<td>HFE-S65C</td>
<td>T</td>
<td>A A</td>
<td>N/A</td>
<td>Blood, 1999</td>
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</tbody>
</table>

Your patient's genetic results

To estimate your patient's risk, we looked at three places in your patient's genome that are associated with hereditary hemochromatosis. These three SNPs are all in the same gene and act in combination to indicate your patient's risk level. The table above shows your patient's markers. Your patient's markers indicate that he/she is at extremely low risk for hemochromatosis. Specifically, he/she has no risk markers present (non-carrier).

The genetics of HFE-related hemochromatosis

Having certain genetic variants, or risk markers, causes hereditary hemochromatosis. Your patient's vulnerability to both genetic and lifestyle risks may vary depending on ancestry, family history and gender.

Our test checks for three variations in the HFE gene, which code for a protein found on the surface of intestinal, liver and some immune system cells. This protein regulates the absorption of dietary iron in the small intestine. HFE may also control another protein called hepcidin, which helps ensure that the body doesn't absorb and store too much iron.

Having two copies of the variation known as C282Y confers the greatest likelihood of developing iron overload. The odds are much lower if a person has a single copy of C282Y plus at least one copy of the H63D or S65C variations, or two copies of H63D.

And the odds are lower still if a person has one copy of H63D or one or two copies of the S65C variation.

- If your patient has two or more copies of either the C282Y, H63D, or S65C markers, in any combination, he or she has two or more risk markers present. In addition, your patient's biological relatives may benefit from knowing that these markers are running in their family.
- If your patient has a single copy of either the C282Y, H63D, or S65C marker, he or she is a HFE gene variant “carrier”, and his or her biological relatives may benefit from knowing that these markers are running in their family.
- If your patient has no copies of either the C282Y, H63D, or S65C markers, he or she is a HFE gene variant “non-carrier”. However, your patient's non-carrier status does not rule out HFE mutations in his or her family members.

Knowing from your patient's DNA profile that he or she has an increased chance of developing hereditary hemochromatosis can alert you to take action. Together, you can take steps to help prevent or minimize long-term organ damage from iron overload.

Clinical note

At any given time people at genetic risk for hemochromatosis can still have normal iron levels (transferrin saturation and serum ferritin) due to their age, sex, and environmental factors. Consideration should be given to confirming a positive Navigenics screen for hemochromatosis with a standard HFE gene test in a clinical laboratory. In addition, the U.S. Centers for Disease Control and Prevention recommends transferring saturation screening (http://www.cdc.gov/ncbddd/hemochromatosis/training/family_detection/testing_and_counseling.htm) for patients with elevated genetic risk for hemochromatosis.
Further reading

Prevention


Researchers evaluated the relationship between food, HFE genotype, and iron status by examining a prospective cohort of women aged 35-69 (the U.K. Women's Cohort Study). Postmenopausal women with an iron-rich diet and who had two copies of C282Y variants had the highest blood iron concentrations.


Researchers studied 2,531 UK women with C282Y and H63D hemochromatosis risk variants and concluded that dietary intervention, such as reducing red meat, could be beneficial for women with two copies of the C282Y mutation, but not for women with one copy of C282Y or one and two copies of H63D.


Researchers studied 256 people who had one copy of the HFE-C282Y risk marker and healthy control subjects and concluded that fortifying foods with iron does not risk the health of people with one copy of HFE-C282Y, as they absorb iron at the same rate as the normal population.


Researchers concluded that regular tea drinking with meals reduces the frequency of phlebotomies required.

Tavill, A. Hepatology, vol. 33, p. 1321, May 2001. "Diagnosis and management of hemochromatosis." This article discusses issues in managing this condition, including susceptibility to infections from bacteria in raw fish and shellfish.

Genetics


Burke, W. et al. Genetics in Medicine, vol. 2, p. 271, September/October 2000. "Contribution of different HFE genotypes to iron overload disease: a pooled analysis." Researchers pooled the results of 14 case-control studies and found that having two copies of the C282Y variant creates the largest risk for developing iron overload disease, but that the H63D mutation also confers risk.

Mura, C et al. Blood, vol. 93, p. 2502, April 1999. "HFE mutations analysis in 711 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis." Researchers evaluated a third mutation in the HFE gene, called S65C, and found that it accounted for some mild hemochromatosis cases that could not be accounted for by the previously described C282Y and H63D mutations.

More information

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Lactose intolerance

Your patient's estimated lifetime risk: low risk

<table>
<thead>
<tr>
<th>Gene or location 1</th>
<th>Risk marker 2</th>
<th>Patient's markers 3</th>
<th>Odds ratio 4</th>
<th>Source 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCT-13910</td>
<td>A</td>
<td>A</td>
<td>N/A</td>
<td>Nature Genetics, 2002</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at a place on your patient's genome where a one-letter difference in the genetic code affects your patient's chances of having lactose intolerance. At this location, there are two markers. Only individuals with two copies of the risk marker have increased risk of lactose intolerance. The table above shows your patient's markers. Your patient has fewer than two copies of the risk marker.

The genetics of lactose intolerance

Lactose intolerance is a common condition that results from a genetic variation. We test for a genetic variant that can predict this condition, particularly in people of European descent. We look at a place on the genome where a one-letter difference in the genetic code affects the chances of having lactose intolerance. At this location, there are two markers. Only individuals with two copies of the risk marker have increased risk of lactose intolerance.

This genetic variation “turns off” the production of lactase after infancy. Lactase, an enzyme produced in the intestines, breaks down lactose, the predominant sugar in milk. When the body doesn’t make enough lactase, bacteria in the intestines convert the unabsorbed lactose in the intestine to a gas that can cause diarrhea, abdominal pain and bloating.

Knowing from a DNA profile whether a patient has lactose intolerance can help you and your patient minimize the condition's effects. Understanding personal genetic risks can motivate patients to make dietary changes that could make a real difference in their health and well-being.

Further reading

Genetics

Bersaglieri, T. et al. American Journal of Human Genetics, vol. 74, p. 1111, published online April 26, 2004. "Genetic signatures of strong recent positive selection at the lactase gene." Authors of this study provide new evidence that natural selection for adult lactase tolerance occurred recently, within the past 5,000 to 10,000 years, because of dairy farming and adult milk consumption.


More information

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Lung cancer

Your patient's estimated lifetime risk: 9% (9 per 100)
Average lifetime risk: 6% (6 per 100)

Your patient has 2 of the 2 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRNA3</td>
<td>C</td>
<td>C C</td>
<td>1.81</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

Your patient's genetic results

We looked at one place on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of lung cancer. At this location, there are two markers. The table above shows your patient's markers. Your patient has two of the two risk markers we looked for.

The genetics of lung cancer

Cancer develops when DNA, the body's genetic material, is damaged beyond repair. Often this happens because of exposure to something in the environment, such as tobacco smoke, but people can also inherit DNA that makes them more likely to get lung cancer.

For lung cancer, the main cause is tobacco smoking, but some smokers seem to be more likely than others to develop the disease, perhaps because their genes make them more susceptible. Recent research has shown that certain genetic variants affecting nicotine receptors in the brain raise the chances that young smokers will have trouble kicking the habit as adults. Exactly how smoking and genetic factors interact to cause lung cancer is something scientists are still trying to decipher, but recent research does show a clear connection between a common inherited genetic variation and increased lung cancer risk.

The available data indicate that these results apply primarily to current and former smokers. (It's difficult for scientists to study the causes of lung cancer in people who have never smoked, since the disease is so rare in this group.)

In the study our test relies on most heavily (Amos 2008), the researchers found no association between the genetic variant and lung cancer in non-smokers, though the number of non-smokers was small. Another study, however, (Hung 2008) did show a modest association in non-smokers. An even more recent study (Weiss 2008) provided convincing evidence that the gene variant we test for actually predisposes a person to nicotine addiction, which in turn raises risk for lung cancer.

This genetic variant was not found to predispose to any subtype of lung cancer in particular. Rather, one study (Amos 2008) found the association in populations of non-small cell lung cancer cases only, another (Hung 2008) in subgroup analyses of small cell, squamous cell, and adenocarcinomas, and a third (Thorgeirsson 2008) in a combination of various lung cancer subtypes.

Whether or not you smoke, knowing from your DNA profile that you are at increased risk can help you and your doctor be alert to symptoms and come up with a plan for lowering the part of your risk that is due to environmental exposure.

Further reading

Prevention


Sinner, P. et al. Cancer Epidemiology Biomarkers & Prevention, vol. 15, p. 2359, December 2006. "The Association of Physical Activity with Lung Cancer Incidence in a Cohort of Older Women: The Iowa Women's Health Study." This study of more than 36,000 women found that smokers can reduce their risk of developing lung cancer by being physically active.
smokefree.gov is a one-stop Web site that offers an online "Quit Smoking" guide, access to smoking cessation counselors by phone or through LiveHelp, downloadable booklets and fact sheets and information on research studies that are looking for smokers who are trying to quit. U.S. Department of Health and Human Services: Its 2006 report, "The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General," details the harmful health effects of secondhand smoke and emphasizes the importance of avoiding it.

**Genetics**


Hung, R.J. et al. Nature, vol. 452, p. 633, April 3, 2008. "A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25." This study, published concurrently with the Amos paper, also found that a variation in the same region of chromosome 15 contributes to lung cancer risk.

Thorgeirsson, T.E. et al. Nature, vol. 452, p. 638, April 3, 2008. "A variant associated with nicotine dependence, lung cancer and peripheral arterial disease." This study, published concurrently with the Amos and Hung papers, also found that a variation in the same region of chromosome 15 contributes to lung cancer risk. The authors argue that this is mediated through increased risk of nicotine dependence among carriers of the gene variant.

Weiss, R.B. Plos Genetics, vol. 4, p. e1000125, July 11, 2008. "A Candidate Gene Approach Identifies the CHRNA5-A3-B4 Region as a Risk Factor for Age-Dependent Nicotine Addiction." This study found that a variation in the region of chromosome 15, which had previously been associated with lung cancer risk, is associated with nicotine addiction in people who began smoking before age 16.

**More information**

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Lupus

Your patient's estimated lifetime risk: **0.19% (19 per 10,000)**
Average lifetime risk: **0.26% (26 per 10,000)**

Your patient has *9* of the *26* risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFAIP3</td>
<td>C</td>
<td>C C</td>
<td>1.0</td>
<td>Nature Genetics, 2008</td>
</tr>
<tr>
<td>IRF5.1</td>
<td>A</td>
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<td>Proceedings of the National Academy of Sciences, 2007</td>
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<tr>
<td>DRB1*0301</td>
<td>C</td>
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<tr>
<td>PTPN22</td>
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<td>ITGAM</td>
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<td>STAT4</td>
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<td>1.56</td>
<td>New England Journal of Medicine, 2007</td>
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<td>IRF5.2</td>
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<td>1.44</td>
<td>Proceedings of the National Academy of Sciences, 2007</td>
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<td>C</td>
<td>C C</td>
<td>1.0</td>
<td>European Journal of Human Genetics, 2007</td>
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<tr>
<td>BANK1</td>
<td>C</td>
<td>A G</td>
<td>1.27</td>
<td>Nature Genetics, 2008</td>
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<tr>
<td>KIAA1542</td>
<td>C</td>
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<td>1.28</td>
<td>Nature Genetics, 2008</td>
</tr>
<tr>
<td>PXK</td>
<td>G</td>
<td>G T</td>
<td>1.27</td>
<td>Nature Genetics, 2008</td>
</tr>
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</table>

**Your patient's genetic results**

We looked at 13 places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of lupus. At each location, there are two markers, for a total of 26 possible risk markers. The table above shows your patient's markers. Your patient has nine of the 26 risk markers we looked for.

**The genetics of lupus**

Systemic lupus erythematosus has a large genetic component, but there are still significant environmental factors to be considered.

**Further reading**

**Genetics**


More information

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Macular degeneration

Your patient's estimated lifetime risk: **2.2% (22 per 1,000)**
Average lifetime risk: **3.1% (31 per 1,000)**

Your patient has **7** of the **12** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
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<tbody>
<tr>
<td>LOC387715-S69A</td>
<td>T</td>
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<td>American Journal of Human Genetics, 2005</td>
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<td>CFB</td>
<td>T</td>
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<td>9.8</td>
<td>Nature Genetics, 2006</td>
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<td>C2-E318D</td>
<td>G</td>
<td>G G</td>
<td>7.73</td>
<td>Nature Genetics, 2006</td>
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<td>CFH-Y402H</td>
<td>C</td>
<td>T T</td>
<td>1.0</td>
<td>New England Journal of Medicine, 2007</td>
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<tr>
<td>C3-R80G</td>
<td>C</td>
<td>C G</td>
<td>1.7</td>
<td>New England Journal of Medicine, 2007</td>
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</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at six places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of macular degeneration. At each location, there are two markers, for a total of 12 possible risk markers. The table above shows your patient's markers. Your patient has seven of the 12 risk markers we looked for.

The genetics of macular degeneration

Most of the risk for age-related macular degeneration is inherited — 67 percent. Studies show that possessing certain genetic variants, or risk markers, can lead to an increased chance of developing AMD over the baseline risk of the general population. Scientists have so far identified several common variants that are associated with increased genetic risk for AMD.

These variants can cause your patient's risk for developing AMD to rise steeply, depending if he or she has one or two copies of the marker. We test for variants that, according to our criteria, have a well-established association with AMD. If your patient has an elevated genetic risk for AMD, you may want to consider testing at an age earlier than standard guidelines suggest.

Further reading

Prevention


Genetics

Klein, Robert J. et al. Science, vol. 308, p. 385, April 15, 2005. "Complement factor H polymorphism in age-related macular degeneration." This study was the first to confirm that two common variants of the CFH gene were strongly associated with age-related macular degeneration.


**More information**

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Melanoma

Your patient's estimated lifetime risk: **1.6% (16 per 1,000)**
Average lifetime risk: **2.6% (26 per 1,000)**

Your patient has **0** of the **4** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1R</td>
<td>T</td>
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<td>Nature Genetics, 2008</td>
</tr>
<tr>
<td>ASIP</td>
<td>A</td>
<td>G G</td>
<td>1.0</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Condition alert

Navigenics tests for common markers associated with melanoma. Much less common are single-gene mutations that can lead to the disease and are associated with rare forms of hereditary melanoma, which Navigenics does not test for. If you answer "yes" to any of the following questions, you should consult a Genetic Counselor or dermatologist.

- Have you or anyone in your family had melanoma (especially two or more cases of melanoma in the same person)?
- Do you have a personal or family history of melanoma and pancreatic cancer – either both diagnoses occurring in the same family member or in two different relatives?
- Does anyone in your family have a known mutation in a gene associated with hereditary melanoma?
- Have you been diagnosed with multiple atypical or dysplastic nevi?

Your patient's genetic results

We looked at two places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of melanoma. At this location, there are two markers. The table above shows your patient's markers. Your patient has zero of the four risk markers we looked for.
The genetics of melanoma

Both genetic and environmental factors can raise a person's melanoma risk. One leading environmental factor is excessive exposure to ultraviolet (UV) light. Genes determine the type of melanin a person's body produces. People who produce mostly the form called eumelanin usually have brown or black hair, dark skin that tans easily, and are better protected against damage from UV radiation. People who produce mostly pheomelanin have red or blond hair, freckles, light skin that tans poorly, and less protection from UV damage.

However, melanoma occurs in people of all skin colors, whether they live in the tropics or in cold northern latitudes, and can occur on places on the body that aren't exposed to sunlight. This indicates that factors other than UV light contribute to melanoma risk.

Further reading

Prevention

Cancer Epidemiology Biomarkers & Prevention, vol. 156, p. 1921-1924, October 2007. “Point/Counterpoint: Sunscreen use is a safe and effective approach to skin cancer prevention.” These reviews analyze the evidence for using sunscreen to prevent melanoma and other skin cancers.


Genetics

Brown, K.M. et al. Nature Genetics, advance online publication, May 18, 2008. “Common sequence variants on 20q11.22 confer melanoma susceptibility.” This study found that a variation in a region of chromosome 20 contributes to melanoma risk.

Gudbjartsson, D.F. et al. Nature Genetics, advance online publication, May 18, 2008. “ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma.” This study found that several gene variations contribute to skin cancer risk.

Pharoah, P.D.P. Nature Genetics, vol. 40, p. 817, July 2008. “Shedding light on skin cancer.” This article discusses three studies that found a connection between the risk of melanoma and genetic variation.

More information

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Multiple sclerosis

Your patient's estimated lifetime risk: **0.36% (36 per 10,000)**  
Average lifetime risk: **0.77% (77 per 10,000)**

Your patient has 3 of the 6 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
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<td>A</td>
<td>C C</td>
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<td>PLoS Genetics, 2007</td>
</tr>
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<td>IL7R</td>
<td>C</td>
<td>C T</td>
<td>1.46</td>
<td>Nature Genetics, 2007</td>
</tr>
<tr>
<td>IL2R</td>
<td>C</td>
<td>C C</td>
<td>1.37</td>
<td>New England Journal of Medicine, 2007</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at three places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of multiple sclerosis. At each location, there are two markers, for a total of six possible risk markers. The table above shows your patient's markers. Your patient has three of the six risk markers we looked for.

The genetics of multiple sclerosis

About half the risk of developing multiple sclerosis (MS) is hereditary. Previous studies were only able to make a definite genetic link between multiple sclerosis and the major histocompatibility complex, an area of the genome associated with several autoimmune diseases.

Researchers hypothesize that people of Northern European background have an overrepresentation of certain variants in this area, which may explain their greater susceptibility to MS. Recent genome-wide association studies have revealed another common variant that produces a relatively more modest effect. This is what we test for.

Further reading

Genetics

Gregory, Simon G. et al. Nature Genetics, published online July 29, 2007. "Interleukin 7 receptor alpha chain (IL7R) shows allelic and functional association with multiple sclerosis." This study examined a subset of genes that were associated with an increased risk of multiple sclerosis.


The International Multiple Sclerosis Genetics Consortium. New England Journal of Medicine, published online July 29, 2007. "Risk alleles for multiple sclerosis identified by a genomewide study." This was the first study to scan the entire human genome for multiple sclerosis risk factors.


More information

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based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

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Obesity

Your patient's estimated lifetime risk: 34% (34 per 100)
Average lifetime risk: 32% (32 per 100)

Your patient has 2 of the 4 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTO</td>
<td>A</td>
<td>A T</td>
<td>1.31</td>
<td>Science, 2007</td>
</tr>
<tr>
<td>PCSK1_2</td>
<td>G</td>
<td>C G</td>
<td>1.13</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

Your patient's genetic results

We looked at two places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of obesity. At each location, there are two markers, for a total of four possible risk markers. The table above shows your patient's markers. Your patient has two of the four risk markers we looked for.

The genetics of obesity

Science has identified certain genetic variants or genetic risk markers that increase a person's risk of obesity over the general population's. Several genetic markers for obesity have been discovered near the FTO and PCSK1 genes. These markers individually have a small effect, but when person has several different risk markers, their risk for developing obesity may dramatically increase.

Further reading

Prevention


Fowler, S.P., et al. Obesity, e-published ahead of print June 5, 2008. "Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain." This epidemiological study found an association between drinking artificially sweetened beverages and long-term weight gain. However, the study could not determine whether the beverages caused the weight gain, or whether people who realized they were gaining weight drank more diet sodas to try to stave it off.


Shai I., et al. New England Journal of Medicine, vol. 359, p. 229, July 17, 2008. "Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet." This two-year study found that Mediterranean and low-carbohydrate diets may be good...
alternatives to low-fat diets. Participants on all three diets lost weight, with those who followed the low-carb diet losing the most.

**Genetics**


**More information**

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Osteoarthritis

Your patient's estimated lifetime risk: 47% (47 per 100)
Average lifetime risk: 47% (47 per 100)

Your patient has 3 of the 4 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
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<td>DVWA</td>
<td>C</td>
<td>C C</td>
<td>1.85</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

Your patient's genetic results

We looked at two places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of osteoarthritis. At each location, there are two markers, for a total of four possible risk markers. The table above shows your patient's markers. Your patient has three of the four risk markers we looked for.

The genetics of osteoarthritis

We test for two variants that meet our criteria for being strongly associated with the risk of osteoarthritis. One of these variants has only been studied in Chinese and Japanese populations, so it is not clear how it affects risk for individuals of other ethnicities. We expect that ongoing research will clarify this information for other populations soon.

Further reading

Prevention


Genetics

Kraus, V.B. et al. Osteoarthritis Cartilage, vol. 15, p. 120, February 2007. "The genetics of generalized osteoarthritis (GOGO) study: Study design and evaluation of osteoarthritis phenotypes." This article reports the findings of a study of more than 1,100 families with OA.

Miyamoto, Y. et al. Nature Genetics, vol. 39, p. 529, April 2007. "A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis." This paper showed that a variation in the GDF5 gene may lead to osteoarthritis susceptibility.

Southam, L. and J. Rodriguez-Lopez et al. Human Molecular Genetics Online, July 6, 2007. "A SNP in the 5' UTR of GDF5 is associated with osteoarthritis susceptibility in Europeans and with in vivo differences in allelic expression in articular cartilage." This paper confirmed the findings of the Miyamoto study.
More information

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Psoriasis

Your patient's estimated lifetime risk: **1.8% (18 per 1,000)**
Average lifetime risk: **4.0% (40 per 1,000)**

Your patient has **3** of the **6** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
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<td>American Journal of Human Genetics, 2007</td>
</tr>
<tr>
<td>IL23R</td>
<td>G</td>
<td>G G</td>
<td>2.53</td>
<td>American Journal of Human Genetics, 2007</td>
</tr>
<tr>
<td>IL13</td>
<td>C</td>
<td>C T</td>
<td>1.38</td>
<td>Genes and Immunity, 2008</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at three places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of psoriasis. At each location, there are two markers, for a total of six possible risk markers. Your patient has three of the six risk markers we looked for.

The genetics of psoriasis

Psoriasis is a condition that most commonly affects the skin, but can have variable presentations, including fingernail changes and arthritis. We test for genetic variants that are strongly associated with a heightened risk for developing psoriasis. There are also reports of metabolic syndrome and cardiovascular disease being co-morbidities.

Further reading

Prevention

Setty, A. et al. Archives of Internal Medicine, vol. 167, p. 1670, Aug. 13, 2007. "Obesity, waist circumference, weight change and the risk of psoriasis in women: Nurses' Health Study II." This large study followed more than 78,000 nurses for 14 years and found that those who weighed more were more likely to develop psoriasis.

Genetics


More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Restless legs syndrome

Your patient's estimated lifetime risk: **1.5% (15 per 1,000)**
Average lifetime risk: **4.0% (40 per 1,000)**

Your patient has **2** of the **6** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker 1</th>
<th>Patient's markers 2</th>
<th>Odds ratio 3</th>
<th>Source 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEIS1</td>
<td>G</td>
<td>T T</td>
<td>1.0</td>
<td>Nature Genetics, 2007</td>
</tr>
<tr>
<td>BTBD9</td>
<td>T</td>
<td>C T</td>
<td>1.67</td>
<td>Nature Genetics, 2007</td>
</tr>
<tr>
<td>MAP2k5_LBXCOR1</td>
<td>G</td>
<td>A G</td>
<td>1.11</td>
<td>Nature Genetics, 2007</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

**Your patient's genetic results**
We looked at three places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of restless legs syndrome. At each location, there are two markers, for a total of six possible risk markers. The table above shows your patient's markers. Your patient has two of the six risk markers we looked for.

**The genetics of restless legs syndrome**

Most people with restless legs syndrome exhibit a symptom called periodic limb movements in sleep. One of the RLS variants we test for, which is located on a gene called BTBD9, is also associated with this symptom, even in people who do not meet the diagnostic criteria for RLS.

**Further reading**

**Prevention**

Allen, R. et al. Sleep Medicine, vol. 4, p. 101, March 2003. "Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health." This review article discusses the causes of restless legs syndrome and the criteria used for diagnosis.

Allen, R. and C. Earley. Movement Disorders, June 12, 2007 (published online). "The role of iron in restless legs syndrome." This review article summarizes research showing a link between low iron levels and restless legs syndrome.

**Genetics**


**More information**
The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Rheumatoid arthritis

Your patient's estimated lifetime risk: **12% (120 per 1,000)**
Average lifetime risk: **3.3% (33 per 1,000)**

Your patient has **8** of the **10** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTPN22</td>
<td>A</td>
<td>A G</td>
<td>1.7</td>
<td>American Journal of Human Genetics, 2004</td>
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<tr>
<td>chr6.138007111</td>
<td>C</td>
<td>C C</td>
<td>1.77</td>
<td>Nature Genetics, 2007</td>
</tr>
<tr>
<td>TRAF1</td>
<td>G</td>
<td>G G</td>
<td>1.74</td>
<td>New England Journal of Medicine, 2007</td>
</tr>
<tr>
<td>STAT4</td>
<td>T</td>
<td>G T</td>
<td>1.27</td>
<td>New England Journal of Medicine, 2007</td>
</tr>
</tbody>
</table>

Your patient's genetic results

We looked at five places on your patient's genome where a one-letter difference in the genetic code affects your patient's odds of psoriasis. At each location, there are two markers, for a total of 10 possible risk markers. Your patient has eight of the 10 risk markers we looked for.

The genetics of rheumatoid arthritis

Rheumatoid arthritis is triggered by a combination of genetic and environmental factors. Slightly more than half of the risk of rheumatoid arthritis (53 percent) is inherited. This calculation is derived from studies of twins. Other studies demonstrate that inheriting certain genetic variants, or risk markers, can lead to an increased chance of developing rheumatoid arthritis over the general population.

We test for several common variants that have established associations with rheumatoid arthritis. One variant in particular in the region called the MHC (major histocompatibility complex), an area linked with auto-immunity, significantly raises the risk of developing rheumatoid arthritis if your patient has two copies. While this is an important component of genetic risk for rheumatoid arthritis, Navigenics does not currently include this region in its genetic analysis, as genetic results for this region are not currently reliable enough to meet our scientific standards.

Knowing if your patient has a hereditary predisposition to develop rheumatoid arthritis can enable you to be alert for symptoms and work together with your patient to minimize the effects of this condition.

Further reading

Genetics

Begovich, A.B. et al. American Journal of Human Genetics, vol. 75, p. 330, 2004. "A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis." This paper showed that PTPN22 may increase reactivity of the immune system and therefore increase an individual's chance of developing RA and other autoimmune diseases.


**More information**

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Sarcoidosis

Your patient's estimated lifetime risk: **0.55% (55 per 10,000)**
Average lifetime risk: **1.0% (100 per 10,000)**

Your patient has **0** of the **2** risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker</th>
<th>Patient's markers</th>
<th>Odds ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTNL2</td>
<td>T</td>
<td>C C</td>
<td>1.0</td>
<td>Nature Genetics, 2005</td>
</tr>
</tbody>
</table>

see page 6 for an explanation of this table format

Your patient's genetic results

We looked at one place on your genome where a one-letter difference in the genetic code affects your odds of restless legs syndrome. At each location, there are two markers, for a total of two possible risk markers. The table above shows your markers. You have zero of the two risk markers we looked for.

The genetics of sarcoidosis

Scientists believe sarcoidosis results from a combination of genetic and environmental factors.

Because sarcoidosis causes such varied symptoms, some experts think it is not a single disease. Rather, sarcoidosis is a collection of genetically distinct disorders with a shared disease process – granulomas. And the genes that control sarcoidosis risk may be different than the genes responsible for determining which symptoms occur once the disease is triggered.

Exactly how sarcoidosis develops is not well understood. Researchers suspect that respiratory infections, chemicals or allergens may spark an overzealous immune response in people with a genetic susceptibility. In the U.S., it's most common among people of African and Northern European ancestry.

Clusters of disease in families suggest sarcoidosis risk can be inherited. About two-thirds of the risk of sarcoidosis is due to genetic factors, according to a study of identical twins. In addition, genome studies have identified several genetic variants that increase the risk of developing the disease.

These genetic studies found variants that may be responsible for the differences in symptoms and risk among ethnic groups. But genes are only part of the story. Sarcoidosis also clusters in communities, leading researchers to suspect that exposure to environmental factors helps to determine who gets the disease. Because sarcoidosis commonly starts in the lungs and associated lymph nodes, researchers think the trigger could be an inhaled substance such as bacteria or allergens.

Further reading

Prevention


Genetics


mutation in BTNL2. " This study found that a variation in a region of chromosome 6 contributes to sarcoidosis risk in whites.

More information

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Stomach cancer, diffuse

Your patient's estimated lifetime risk: \textbf{0.45\% (45 per 10,000)}

Average lifetime risk: \textbf{1.7\% (170 per 10,000)}

Your patient has 0 of the 2 risk markers we looked for.

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Risk marker \textsuperscript{2}</th>
<th>Patient's markers \textsuperscript{3}</th>
<th>Odds ratio \textsuperscript{4}</th>
<th>Source \textsuperscript{5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSCA</td>
<td>A</td>
<td>G G</td>
<td>1.0</td>
<td>Nature Genetics, 2008</td>
</tr>
</tbody>
</table>

Your patient's genetic results

We looked at one place on your genome where a one-letter difference in the genetic code affects your patient's odds of diffuse stomach cancer. At this location, there are two markers. The table above shows your patient's markers. Your patient has zero of the two risk markers we looked for.

The genetics of diffuse stomach cancer

Because diffuse stomach cancer is rare, researchers have not figured out exactly what causes it. Strong evidence shows that it is different from other forms of stomach cancer, which tend to stay in one place, forming a discrete tumor.

Some studies have found that the most common trigger of stomach cancer overall, \textit{H. pylori} infection, may also contribute to diffuse stomach cancer. Some people with this infection seem to be more likely than others to develop the disease, perhaps because their genes make them more susceptible to irritation caused by the infection. The same holds true for people who eat diets heavy in smoked, pickled, cured and salted foods.

Recent research shows a clear connection between the common inherited genetic variant we test for and increased risk of diffuse stomach cancer.

In the study our test relies on, researchers showed that, in laboratory tests, this genetic variant seems to affect the growth of cells in the stomach's lining, where diffuse cancer starts. The study found an association between the variant and diffuse stomach cancer among Japanese and Korean people. While it's not possible to say for certain that the variant raises risk for people of other ethnicities, research on other conditions has shown that when this type of a genetic variant is linked to disease in one or two ethnic groups, the connection often holds true for people of other ethnic backgrounds as well.

Further reading

Prevention

Gonzalez, C.A. et al. Journal of the National Cancer Institute, vol. 98, p. 345, March 2006. \textit{"Meat Intake and Risk of Stomach and Esophageal Adenocarcinoma Within the European Prospective Investigation Into Cancer and Nutrition (EPIC)."} This study of more than 500,000 men and women found that eating red meat more than twice a day and eating a lot of cured and smoked meat increased the risk of stomach cancer, especially among people infected with \textit{H. pylori} bacteria.

Hansen, S. et al. Gut, vol. 56, p. 918, 2007. \textit{"Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status."} This study showed that some diffuse stomach cancers are associated with \textit{H. pylori} infection.
National Cancer Institute: Its information summary, *Stomach (Gastric) Cancer Prevention (PDQ®)*, provides a quick, easy-to-read overview of stomach cancer facts and prevention strategies.

Tsugane, S., and S. Sasazuki. Gastric Cancer, vol. 10, p. 75, June 2007. “Diet and the risk of gastric cancer: Review of epidemiological evidence.” This review of research linking diet and stomach cancer found that a high intake of preserved foods and salt increased cancer risk, while eating lots of fruit and vegetables, particularly fruit, lowered risk.


**Genetics**

The Study Group of Millennium Genome Project for Cancer. Nature Genetics, advance online publication, May 18, 2008. “Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer.” This study found that a variation in a region of chromosome 8 contributes to stomach cancer risk.

**More information**

The above information represents a condensed version of your patient's results, abridged to highlight information most important to physicians. Your patient's versions of these results contain further information, such as suggested evidence-based prevention measures to consider and additional scientific details. Your patient can also provide you with this version of his/her results.

If you have any questions, please contact a Navigenics Genetic Counselor by calling (866) 522-1585 / +1 (650) 585-7743 between the hours of 9am and 5pm PST, Monday through Friday.
Abacavir

Your patient's risk of side effects: low risk

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Test SNP</th>
<th>Patient's markers</th>
<th>Scientific name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B</td>
<td>rs2395029</td>
<td>TT</td>
<td>not HLA-B*5701</td>
<td>low risk</td>
</tr>
</tbody>
</table>

Navigenics uses a single SNP (rs2395029) as a proxy for HLA-B*5701.

Your patient's results

We looked at one place in your patient's genetic code where a one-letter variation, called a SNP, affects your patient's odds of having potentially life-threatening abacavir side effects (hypersensitivity reaction). This site is located in the HLA region.

The table above shows your patient's results, and your patient's genetic markers are TT. What this means for your patient is that, based on these genetic markers, your patient is likely to have a low risk of side effects since your patient carries no copies of the risk-related HLA-B*5701 variant.

Side effects include life-threatening allergic reaction (hypersensitivity) with the following symptoms: fever, rash, nausea, vomiting, diarrhea, stomach pain, extreme tiredness or achiness, shortness of breath, cough or sore throat.

Since it is difficult to directly test the HLA-B*5701 variation, your patient's test looked at a well-established, reliable proxy for this variation. It is important to know that for some people of Asian ancestry (specifically Han Chinese), this proxy may not be the most accurate way to assess for abacavir side effects. If you have questions, please contact a Navigenics Genetic Counselor (please call the phone number at the top of this page).

Drug details

**Brand names:** Epzicom®, Kivenxa®, Trizivir®, Ziagen®

**Primary uses:** Abacavir is approved by the FDA for treating HIV infection.

The genetics of abacavir side effects

The mechanism by which abacavir causes severe hypersensitivity reactions is poorly understood. Several studies point to an immunological basis for this reaction. The human leukocyte antigen (HLA) genes are a crucial part of the human immune system and variants within the HLA-B gene have been associated with hypersensitivity reactions and immune disease. It is believed that hypersensitivity reaction is triggered when an HLA-encoded molecule presents the drug (abacavir) for T-cell activation, causing the release of inflammatory cytokines and chemokines, which in turn initiates a cascade of immune events leading to the clinical features of hypersensitivity reaction. Because not all individuals who are HLA-B*5701 positive and taking abacavir experience hypersensitivity, this particular gene variant is said to be necessary but not sufficient for hypersensitivity manifestation.

Navigenics tests for a single SNP, located on chromosome 6, shown to increase the odds of life-threatening hypersensitivity reactions to abacavir therapy. This SNP is a proxy for the HLA-B*5701 risk variant. Large randomized control trials have demonstrated that screening for HLA-B*5701 reduces the risk of hypersensitivity reactions to abacavir (48 percent sensitivity, 97 percent specificity per Mallal, 2008) by effectively identifying individuals whose genetic profile, or genotype, puts them at increased risk prior to initiation of abacavir therapy. This research prompted the FDA to recommend genetic screening for this variant prior to initiation or re-initiation of abacavir therapy. Given that we know approximately six percent of the general population carries the HLA-B*5701 variant, abacavir genetic pre-screening of 100 patients would prevent approximately four cases of hypersensitivity while contraindicating the use of abacavir in two HLA-B*5701–positive patients who would have likely tolerated the drug.
Also of interest, the HLA-B*5701 SNP used in the Navigenics test has been implicated in another medication side effect: drug-induced liver injury to the antibiotic floxacillin. For both of these medications, Navigenics uses a well-established, reliable genetic proxy for this variation since it is difficult to directly test the HLA-B*5701 variation. This is especially important to note for people with Asian ancestry (specifically identified in Han Chinese), because this proxy may not be the most accurate way to assess for abacavir side effects in this population.

Clinical notes

The FDA recommends that physicians avoid prescribing abacavir to people carrying the HLA-B*5701 risk variant. A negative HLA-B*5701 screening test does not rule out abacavir hypersensitivity reaction, but the likelihood of such an immunologically proven event is very low. The following suggestions represent current clinical understanding and practices to date:

Follow-up testing

Although your patient does not carry the risk variant included in this test, you may want to consider follow-up testing to better understand how your patient's genetic makeup affects his/her response to abacavir, especially if he/she is of Chinese ancestry. The type of genetic testing offered by Navigenics may be somewhat less conclusive for people of Chinese descent. There are many labs that offer direct HLA typing. For more information, see the links below or contact a Navigenics Genetic Counselor (please call the phone number at the top of this page):

- LabCorp > (www.labcorp.com/wps/portal/lut/p/c0/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hACzO_QCM_IwMLo1ALAYnj1yBnQxMfAwmL_i_2CbEdFAAnGmcI/?WCM_PORTLET=PC_7_Ue4sl93089S102JGM1M2N)
- Quest Diagnostics > (www.questdiagnostics.com/brand/business/hla_immu_gen/test_menu.html)

Personalized treatment

- **If your patient needs anti-HIV therapy, abacavir may be a good choice.** Life-threatening hypersensitivity reactions to abacavir usually occur within the first six weeks of starting therapy. If your patient has been on abacavir for a few months and has not experienced clinical signs of abacavir hypersensitivity, your patient's risk for these side effects is very low.

- **Avoid lapses in abacavir therapy.** Abacavir hypersensitivity reactions are more common in abacavir-tolerant individuals who discontinue and then resume abacavir therapy. For this reason, it is recommended that those already taking abacavir continue with the therapy until a hypersensitivity reaction is medically confirmed. Early discontinuation may eliminate the potential to use this drug for anti-retroviral therapy in the future.

- **Be aware of concurrent drug use that can increase the risk of hypersensitivity reaction.** These include protease inhibitors and other NRTI drugs.

More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have any questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Beta blockers

How effective for your patient: **typical effectiveness**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient’s results</th>
<th>Scientific name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location¹</td>
<td>Test SNP²</td>
<td>Patient’s markers³</td>
<td></td>
</tr>
<tr>
<td>GRK5</td>
<td>rs17098707</td>
<td>AA</td>
<td>typical effectiveness</td>
</tr>
</tbody>
</table>

see page 8 for an explanation of this table format

**Your patient’s results**

There is a class I indication for beta-blocker treatment in heart failure. However, individual responses to beta blocker treatment vary widely, and there is a need to identify decreased responders within the broader clinical group. G protein-coupled receptor kinases (GRKs) regulate and desensitize beta adrenergic receptors, suggesting that genetic GRK variants might modify outcomes in cardiac failure and ischemia. In order to assess your patient’s expected responsiveness to beta blocker medications, we genotyped a single location in the GRK5 gene, known to influence beta blocker response and level of effectiveness.

The table above shows your patient’s results, and that your patient’s genetic markers are AA. What this means for your patient is that, based on these markers, your patient is likely to be responsive to beta blockers, and these drugs are more likely to be effective. People who carry two copies of the “A” marker are more likely to respond to beta blockers.

**Drug details**

**Brand names:** Betapace®, Blocadren®, Brevibloc®, Coreg®, Coreg CR®, Inderal®, InnoPran XL®, Lopressor®, Sectral®, Tenormin®, Toprol XL®, Visken®, plus others less commonly prescribed

**Primary uses:** Common primary uses include cardioprotection after a heart attack, hypertension, arrhythmia, glaucoma, migraine, and other conditions.

**The genetics of beta blocker effectiveness**

Beta blockers exert their effects by blocking a cardiac signaling pathway (the beta-adrenergic pathway, beta-AR). This pathway helps determine how a person's heart functions, and the pathway is affected, in part, by a gene called GRK5.

A particular variant of GRK5 (Gln41Leu), common in African Americans, reduces beta-AR signaling, meaning that the variation acts as a genetic beta-blocker. In other words, people with the altered gene essentially make their own version of beta blockers all the time. People with this GRK5 gene variant respond less well to beta blockers after heart failure. This may explain why clinical trials of beta blockers in heart failure have generally shown less promising results in African-Americans than in European-Americans.

A large number of genes have been investigated to see if they influence the effectiveness of beta blockers and other hypertension drugs. These include ACE, ADD1, ADRB1, ADRB2, AGT, AGTR1, and many others. These studies have yielded inconsistent results, and these genes are not currently included in the Navigenics service.

**Clinical notes**

Professional organizations have yet to set guidelines on how physicians should incorporate genetic information into clinical decision-making on this drug. The following suggestions represent current clinical understanding and practices to date:

**Treatment considerations**

Since your patient's genetic results indicate that he/she has a typical response to beta blockers after heart failure, you may want to consider prescribing beta blockers. Additionally:
• **Use your patient's genotype, rather than race, to optimize hypertension treatment.** It has long been known that African-Americans as a group respond less favorably to beta blocker treatment. However, the study confirming a link between this genetic result and beta blocker response indicates that about 60 percent of African Americans have an unaltered gene and thus may actually benefit from beta blocker treatment.

• **Evaluate this entire class of drugs.** These results apply to any beta blockers used to treat heart failure, including carvedilol and metoprolol.

### More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Carbamazepine

Your patient's risk of side effects: unable to be determined

<table>
<thead>
<tr>
<th>Gene or location</th>
<th>Test SNP</th>
<th>Patient's markers</th>
<th>Scientific name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B</td>
<td>rs2844682</td>
<td>AG</td>
<td>unable to be determined</td>
<td>unable to be determined</td>
</tr>
<tr>
<td></td>
<td>rs3909184</td>
<td>CG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

see page 8 for an explanation of this table format

Your patient's results

We looked at two places in your patient's genetic code where one-letter variations, called SNPs, affect your patient's odds of severe carbamazepine side effects. Both of these variations are in the HLA region.

The table above shows your patient's results, and your patient's genetic markers are AG/CG. However, we are unable to determine what this means for your patient. In order to have the HLA-B*1502 genotype that is associated with carbamazepine side effects, a person must have at least one copy of both of the risk markers tested, like your patient, but those markers need to have been inherited from the same parent. The test performed by Navigenics cannot determine whether these two risk markers were inherited from the same parent or not. You and your patient may want to consider a follow-up test using HLA sequencing to determine your risk level for carbamazepine side effects.

Side effects include severe life-threatening dermatological symptoms associated with Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). SJS and TEN symptoms include fever, body aches, rash, blisters on mucous membranes, and small (SJS) or large (TEN) areas of peeling skin.

IMPORTANT: HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). While HLA-B*1502 is seen among a wide range of Asian populations, the genetic analysis method used in this test is most relevant to people of Han Chinese ancestry. The testing method does not accurately represent HLA-B*1502 in individuals with African ancestry, and research has not shown whether or not it is an accurate representation in other groups, including Caucasians and Japanese.

Drug details

Brand names: Carbatrol®, Epitrol®, Equetro®, Tegretol®, Tegretol XR®,

Primary uses: Approved by the U.S. Food and Drug Administration for treatment of epilepsy, neuropathic pain, and certain psychiatric conditions, including bipolar disorder and schizophrenia

Secondary uses: Treatment of attention-deficit/hyperactivity disorder (ADHD)

The genetics of carbamazepine side effects

The mechanism by which carbamazepine causes severe skin reactions is poorly understood. Several studies point to an immunological basis for this toxicity. The human leukocyte antigen (HLA) genes are a crucial part of the immune system, and variants within the HLA-B gene have been linked to hypersensitivity reactions and immune disease.

Navigenics uses the combined genetic profile, or genotype, at two SNPs that tag the HLA region to determine whether an individual carries the HLA-B*1502 haplotype/risk variant. The odds of adverse severe skin reactions with carbamazepine therapy are significantly greater in people who carry the HLA-B*1502 variant. Testing for this variant can be challenging because, in order to be at risk, a person needs to have at least one copy of both of the risk markers tested (rs2844682 and rs3909184), and they need to have inherited those markers from the same parent. In a small percentage of people, additional testing using direct HLA sequencing is required to determine their risk.

This particular HLA-B*1502 variant occurs almost exclusively in people of Asian ancestry, which is why the FDA recommends genetic screening for HLA-B*1502 before people of Asian ancestry begin treatment with carbamazepine.
Other factors that influence the chance of carbamazepine side effects include certain health status risk factors. According to the FDA, notable variation exists in the prevalence of HLA-B*1502 across Asian populations. Specifically:

- Ten to 15 percent or more of patients may carry the allele in parts of China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan.
- South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging about two to four percent of patients, but higher in some sub-groups.
- HLA-B*1502 appears to be present at a low frequency (less than one percent of the population) in Japan and Korea.

**Clinical notes**

According to the FDA and the drug manufacturer, carbamazepine therapy is contraindicated for patients carrying the HLA-B*1502 risk variant (www.accessdata.fda.gov/drugsatfda_docs/label/2007/016608s098lbl.pdf). The following suggestions represent current clinical understanding and practices to date:

**Treatment considerations**

Because your patient's genetic risk for carbamazepine side effects was unable to be determined from this test, you may want to order follow-up testing to resolve this uncertainty. Find more information about the HLA sequencing method here (www.mayomedicallaboratories.com/test-catalog/print.php?unit_code=89347), or by going here (www.labcorp.com/wps/portal/provider/testmenu) and searching on the term “HLA B*1502 Carbamazepine Sensitivity”.

You may also want to consider speaking with a Navigenics Genetic Counselor about follow-up testing and what clarity it can provide (please call the phone number displayed at the top of this page.

**Other risk factors**

Certain patient health status factors may also affect your patient's risk of side effects, including:

- Certain illnesses, including diabetes and glaucoma, have been associated with increased risk
- Gender, with females at greater risk
- Dose, with higher dose conferring increased risk

**More information**

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
**Clopidogrel**

How effective for your patient: **typical effectiveness**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>Scientific name</th>
<th>What it means</th>
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<tbody>
<tr>
<td>Gene or location¹</td>
<td>Test SNP²</td>
<td>Patient's markers³</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>rs4244285</td>
<td>GG</td>
<td>*1/*1</td>
</tr>
<tr>
<td></td>
<td>rs4986893</td>
<td>GG</td>
<td>typical effectiveness</td>
</tr>
</tbody>
</table>

see page 8 for an explanation of this table format

**Your patient's results**

We looked at two places in your patient's genetic code where one-letter variations, called SNPs, can affect your patient's response to clopidogrel. Both of these variations are in a gene called CYP2C19.

The table above shows your patient's results, and your patient's genetic markers are *1/*1. What this means for your patient is that, based on these markers, clopidogrel is likely to be an effective medication. Specifically, your patient has no risk variants related to reduced clopidogrel effectiveness, and is therefore likely to have a typical response to clopidogrel. This drug is likely to be an effective therapy.

Please note, however, that there are other genetic factors that are not included in this test that can impact how effective clopidogrel may be for your patient.

**Drug details**

**Brand names:** Plavix®

**Primary uses:** Common primary uses include prevention of recurrent ischemic events after an acute coronary syndrome or a percutaneous event.

**The genetics of clopidogrel effectiveness**

Clopidogrel (Plavix) is prescribed for a wide spectrum of cardiovascular disease and acute coronary syndromes. It is also used for patients undergoing angioplasty or similar procedures to treat narrowed coronary arteries. As clopidogrel is a "pro-drug," it requires hepatic bioactivation by the CYP450 system before it can exert its anti-clotting effects. One protein which enables this bioactivation is CYP2C19 (pronounced “sip-2-C-19”).

Several variants in the CYP2C19 gene are known to reduce CYP2C19 protein function. Navigenics tests for two of the most common CYP2C19 variants: CYP2C19*2 (rs4244285) and CYP2C19*3 (rs4986893). Both of these “loss of function” variants result in a less efficient CYP2C19 protein and have been associated with clopidogrel resistance. People with two loss of function variants can be considered poor clopidogrel metabolizers, while people with one loss of function variant can be considered intermediate clopidogrel metabolizers. In this test, individuals with no identifiable *2 or *3 (“pronounced “star 2” and “star 3”) variants are considered to have the normal, functional version of the gene called CYP2C19*1. This is important to note because, though less common, other CYP2C19 variants can impact the function of the CYP2C19 protein. These variants are more commonly found in people of African descent and East Asians than in Caucasians, and as a result, patients with African or East Asian ancestry may want to consider follow-up testing.

Studies have also shown that people carrying the CYP2C19 *2 or CYP2C19*3 risk variants are less responsive to clopidogrel, resulting in more serious cardiac events, such as heart attack, stroke, or death from cardiovascular causes. These people also have a greater risk of developing a blood clot in or near cardiac stents. This risk also appears to be more pronounced in patients under the age of 45.

Preliminary recent studies have also demonstrated that additional genetic variants, such as CYP3A4, CYP2B6, and ABCB1, may also play an important role in decreased clopidogrel effectiveness. The Navigenics service does not include these variants at this time.
Clinical notes

The U.S Food and Drug Administration advises that physicians consider modifying treatment plans for patients having genetic variants linked to a reduced ability to metabolize clopidogrel. Additionally, the FDA has added a drug warning label (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm) stating potential adverse drug interactions between clopidogrel and other drugs metabolized by CYP2C19, and says that CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel.

The following suggestions represent current clinical understanding and practices to date:

- Studies have shown that in individuals who carry variants that decrease CYP2C19 protein function, such as the variants included in this test, 30 percent less clopidogrel reaches the target tissues in the body (at both initial treatment and maintenance doses). In other words, the risk variants reduce active levels of clopidogrel.

- Individuals being treated with clopidogrel who carry at least one CYP2C19*2 risk variant (compared to those with no risk variants) experience 1.4-fold greater rate of heart attack, stroke, or morbidity from cardiovascular causes and 3.3-fold higher rate of stent thrombosis.

Treatment considerations

Since your patient's genetic results indicate that he/she is likely to have a typical response to clopidogrel, you may want to consider prescribing this medication. Additionally, you may want to:

- **Consider follow-up testing.** If you prescribe clopidogrel for this patient now or in the future, consider a follow up test (platelet reactivity testing) to see how effectively the drug is working. Factors beyond the genetic variants analyzed in this test may also affect clopidogrel effectiveness.

- **Consider drug-drug interactions.** Avoid prescribing clopidogrel with other drugs that can further reduce clopidogrel response by reducing CYP2C19 enzyme activity. This includes proton pump inhibitors (PPI's). Some studies suggest that PPI's reduce clopidogrel effectiveness by inhibiting CYP2C19. H2 blockers are a possible alternative for relieving stomach irritation in patients taking clopidogrel (with the exception of cimetidine, a CYP2C19 inhibitor). Other drugs that are also potent inhibitors of the CYP2C19 enzyme would be expected to have a similar effect and should be avoided in combination with clopidogrel. These include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Floxacillin

Your patient's risk of side effects: **low risk**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>Scientific name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location</td>
<td>Test SNP</td>
<td>Patient's markers</td>
<td></td>
</tr>
<tr>
<td>HLA-B</td>
<td>rs2395029</td>
<td>TT</td>
<td>not HLA-B*5701</td>
</tr>
</tbody>
</table>

Navigenics uses a single SNP (rs2395029) as a proxy for HLA-B*5701.

**Your patient's results**

We looked at one place in your patient's genetic code where a one-letter variation, called a SNP, affects your patient's odds of floxacillin side effects. This site is located in the HLA region.

The table above shows your patient's results, and your patient's genetic markers are TT. Based on these genetic markers, your patient is likely to have a low risk of side effects since he/she has no copies of the risk-related HLA-B*5701 variant. Side effects include liver toxicity.

Since it is difficult to directly test the HLA-B *5701 variation, this test looked at a well-established, reliable proxy for this variation. It is important to know that for some people of Asian ancestry (specifically Han Chinese), this proxy may not be the most accurate way to assess the HLA-B*5701 variant. If you or your patient have questions, contact a Navigenics Genetic Counselor (please call the phone number at the top of this page).

**Drug details**

**Brand names:** Floxapen®, Fluclox®, Sesamo®

**Primary uses:** Used to treat a wide range of staphylococcal infections throughout the body, as well as to prevent infection during major surgical procedures

**The genetics of floxacillin side effects**

At present, the mechanism by which floxacillin causes liver toxicity is poorly understood. But several studies point to an immunological basis for this toxicity. The human leukocyte antigen (HLA) genes are a crucial part of the human immune system and variants within the HLA-B gene have been associated with hypersensitivity reactions and autoimmune disease.

Navigenics tests for a single HLA variant shown to increase the odds of liver toxicity with floxacillin therapy: the HLA-B*5701 risk variant. Other factors that influence your patient's sensitivity to floxacillin include certain health status risk factors (see Clinical Notes section for further detail). Since it is difficult to directly test the HLA-B *5701 variation, your patient's test looked at different location in the genetic code that serves as a well-established, reliable genetic proxy for this variation. It is important to know that for some people of Asian ancestry (specifically identified in Han Chinese), this proxy may not be the most accurate way to assess for HLA-B*5701 genotype. If you have questions, contact a Navigenics Genetic Counselor (please call the phone number at the top of this page).

**Clinical notes**

As yet, professional organizations have yet to set guidelines on how physicians should incorporate genetic information into clinical decision-making on this drug. The following suggestions represent current clinical understanding and practices to date:

**Factors influencing your patient's side effects profile**
Ancestry considerations: Navigenics tests for a single SNP that tags HLA-B*5701 (rs2395029). This SNP is an excellent predictor of floxacillin sensitivity in most people. For a subset of people of Asian ancestry (Han Chinese), however, the Navigenics floxacillin sensitivity test will be less accurate. See the “Genetics of floxacillin side effects” section for more information.

Treatment considerations

Since your patient's genetic results indicate that he/she is at low risk, you may not want to consider alternate therapies or procedures to prevent floxacillin-induced liver toxicity.

Follow-up testing

Since the Navigenics test does not directly assess the HLA-B*5701 haplotype, for some patients, especially those with Asian ancestry, additional genotyping may be appropriate to most accurately determine your patient's risk. Currently, no labs in the United States offer HLA genotyping in relation to floxacillin use. However, the genetic testing to assess sensitivity to another drug, abacavir, uses the same assay and a test for this marker is widely available. Options include:

- LabCorp > (https://www.labcorp.com/wps/portal/lut/p/c0/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hACzO_QCM_IwMLo1ALAyNj1yBnQxNfAwM_I_2CbEdFAAnCgbmcl/?WCM_PORTLET=PC_7_U4E4S193089S102JGM1M2N
- Quest Diagnostics > (www.questdiagnostics.com/brand/business/hla_immu_gen/test_menu.html)

Other risk factors

Certain patient health status risk factors may also affect your patient's risk of side effects, including:

- Age, with those over 60 at greater risk
- Gender, with females at greater risk
- Duration of floxacillin treatment, with those on the drug longer at greater risk

More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Fluorouracil

Your patient's risk of side effects: low risk

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location</td>
<td>Test SNP</td>
<td>Scientific name</td>
</tr>
<tr>
<td>DPYD</td>
<td>rs3918290</td>
<td>*1/*1</td>
</tr>
</tbody>
</table>

Your patient's results

Based on your patient's genetic markers, your patient is likely to have a low risk of side effects. These can include severe, potentially fatal, toxicity including diarrhea, other gastrointestinal disorders, and decreased white blood cell count.

We determined your patient's risk by analyzing your patient's DNA. Specifically, we looked at one place in your patient's genetic code where a one-letter variation, also known as a SNP, affects your patient's odds of severe side effects after fluorouracil treatment. This site is located in the DPYD gene.

The table above shows your patient's results, and your patient's genetic markers are CC, also called *1/*1 (pronounced "star one/star one"). What this means for your patient is that, based on these genetic markers, your patient has no copies of the genetic marker related to an increased risk for fluorouracil side effects and is therefore at low risk.

Drug details

**Brand names:** Adrucil®, Efudex®, Fluorplex®, and Xeloda® (related prodrug)

**Primary uses:** Approved by the FDA for the treatment of breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, basal cell carcinoma and actinic keratosis.

**Secondary uses:** Treatment of other types of cancers; glaucoma, during and after certain surgery (trabeculectomy).

The genetics of fluorouracil side effects

The DPYD gene, located on chromosome 1p22, is named for the protein it regulates, DPD (dihydropyrimidine dehydrogenase). Some DPYD gene variants cause DPD enzyme deficiency, resulting in a toxic build-up of fluorouracil in the body. There are over 30 known variants in the DPYD gene. Navigenics tests for the most common DPYD deficiency variant, called DPYD*2A, which accounts for roughly 50 percent of the known DPYD deficiency mutations.

This DPYD variant causes an entire segment of the gene to be skipped when the gene is translated, so that the final DPD protein is non-functional. Due to the decrease in active DPD enzyme production, people with this DPYD variant have been shown to have higher odds of developing a range of severe adverse events upon treatment with fluorouracil and similar drugs. Whether an individual carries one or two copies of this variant will affect the level of active enzyme. Other, less common DPYD variants (for which Navigenics does not test) can also raise an individual’s risk for severe toxicity reactions to fluorouracil, as can variants in other genes, including TYMS, and several personal health factors.

This result also does not include analysis of a gene called MTHFR, as its significance is less established.

Clinical notes

According to the FDA and the drug manufacturer, fluorouracil and capecitabine therapy are contraindicated for patients with known DPD deficiency. This genetic test is able to identify the most common cause of such DPD deficiency. In addition to genetic testing, there are additional ways to assess your patients current DPD enzyme activity level. Profound DPD deficiency can be detected by uracil and/or thymine levels in plasma or urine. However, to detect the more prevalent partial DPD deficiency, the standard lab method is a direct measurement of DPD enzyme activity using a radioenzymatic assay. For real-time analysis of DPD enzyme activity, the newly developed uracil breath test (UBT) can accurately
distinguish patients with normal versus deficient enzyme activity. The following suggestions represent current clinical understanding and practices to date:

**Follow-up testing**

Although your patient does not carry the risk variant included in this test, other genes may also increase the risk of fluorouracil toxicity. You may consider additional testing to determine whether your patient carries a risk variant in the TYMS gene (for which Navigenics does not currently test). For an overview of options for follow-up testing, visit:

- [Myriad Genetics >](#)
- [ARUP Laboratories >](#)

**Other risk factors**

Certain patient health status factors may also affect your patient's risk of side effects, including:

- Dose, with higher dose conferring increased risk
- Route of administration, with greater risk when the drug is given via IV bolus administration compared to continuous IV infusion or topical treatment
- Ancestry, with African-Americans having greater prevalence of DPD protein deficiency than Caucasians. Research indicates that there is some other variant in this gene or another gene which leads to the increased frequency of DPD deficiency in this population
- Gender, with females at greater risk
- Age, with older individuals experiencing more risk
- Skin health (for topical formulations), where risk is greater when drug comes in contact with inflamed or ulcerated skin

**More information**

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
**Irinotecan**

Your patient's risk of side effects: **moderate risk**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>Scientific name</th>
<th>What it means</th>
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</thead>
<tbody>
<tr>
<td>Gene or location</td>
<td>Test SNP</td>
<td>Patient's markers</td>
<td></td>
</tr>
<tr>
<td>UGT1A1</td>
<td>rs10929302</td>
<td>AG</td>
<td>moderate risk</td>
</tr>
</tbody>
</table>

**Your patient's results**

We looked at one place in your patient's genetic code where a one-letter variation, called a SNP, affects your patient's odds of severe irinotecan side effects. This site is located in the UGT1A1 gene. The table above shows your patient's results, and your patient's genetic markers are AG. What this means for your patient is that, based on these markers, your patient is likely to have a moderate risk for severe side effects with irinotecan therapy, including immunosuppression and diarrhea.

However, it's important to note that your patient's genetic results also relate to the effectiveness of this drug. This drug, given at standard doses, may actually be somewhat more effective for people with your patient's genetic profile. Should your patient ever need cancer treatment, you may want to weigh the risk of side effects against the potential benefits of this medication. Please see the "Genetics of irinotecan side effects" section on this page for more details.

**Drug details**

**Brand names:** Campto®, Camptosar®

**Primary uses:** Irinotecan is approved by the U.S. Food and Drug Administration for first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) and leucovorin and second-line treatment for colon cancer following 5-FU-based therapy.

**Secondary uses:** Irinotecan is also used as second-line treatment for non-small-cell lung and other forms of cancers such as breast cancer, though such additional uses have not necessarily been approved by the FDA.

**The genetics of irinotecan side effects**

The UGT1A1 gene, located on chromosome 2, encodes the enzyme uridine disphosphate glucuronosyl transferase 1 (UGT1A1), which metabolizes irinotecan by inactivating the activated form of irinotecan (known as SN-38). Individuals who carry the risk-related UGT1A1 gene variant have lower than average levels of this enzyme and will break down the drug more slowly than individuals who have no copies of the risk variant. Because the drug lingers longer in the systems of people with one or more copies of the risk variant, they are likely to experience greater benefit from the drug (in terms of tumor reduction), but are more prone to adverse effects of the drug, such as diarrhea and neutropenia.

The most commonly studied variant in the UGT1A1 gene is known as UGT1A1*28, and consists of a variable number of repeats of the nucleotides T and A. More recent papers indicate that a single SNP, rs10929302, is actually a better predictor of irinotecan toxicity, and this is what the Navigenics test measures. However, this genetic variant alone does not explain all cases of irinotecan side effects, and therefore other genetic factors likely play a role. Specifically in Asian populations, another variant UGT1A1*6 has been associated with clinical outcomes. UGT1A1 is also important in the metabolism of bilirubin. Other less common mutations in the UGT1A1 gene can cause clinically relevant diseases, including Gilbert's syndrome and Crigler-Najjar syndrome.

Of note, in the Caucasian population Gilbert's syndrome is most commonly caused by the UGT1A1*28 variant. These patients show a reduced expression of the UGT1A1 enzyme resulting in lower rates of bilirubin, as well as SN-38 glucuronidation (the process by which substances such as drugs are converted to forms that can be excreted from the body).

It's also important to note that this gene relates to the effectiveness of irinotecan. This drug, given at standard doses, is actually likely to be more effective for people with one or two copies of the risk variant. In such cases, physicians and
Clinical notes

The FDA recommends that physicians consider a reduced initial irinotecan dose for patients known to carry two copies of the UGT1A1*28 risk-related variant and suggests that patients with one copy may also be at increased risk for serious side effects with this drug. The following suggestions represent current clinical understanding and practices to date:

Follow-up testing

Because your patient’s genetic results indicate that he/she is at moderate risk for severe irinotecan side effects, you may want to order follow-up confirmatory testing. Numerous clinical laboratories offer follow-up testing. If you have questions about follow-up testing, please contact a Navigenics Genetic Counselor.

Personalized treatment

You may want to tailor your patient’s therapy to reduce the risk of severe irinotecan side effects. Treatment options include:

- **Reducing your patient’s dose.**
- **Considering other drugs.** Possibilities include cetuximab or bevacizumab, based on medical factors and patient preference.
- **Treating patient with colony-stimulating factors.** This treatment is recommended before the first cycle of chemotherapy to prevent the occurrence of immune system suppression with fever. Such treatments are currently recommended by the National Comprehensive Cancer Network for patients with a 20 percent or greater risk of febrile neutropenia (immune system suppression with fever).
- **Weighing risks and benefits of this medication.** It’s important to note that your patient’s genetic results also relate to the effectiveness of this drug. This drug, given at standard doses, may be more effective for people with your patient’s genetic profile. Should your patient ever need cancer treatment, you may want to weigh your patient’s risk of side effects against the potential benefits of this medication.

Other risk factors

Certain patient health status factors may also affect your patient’s risk of side effects, including:

- Age, with older individuals at greater risk
- Prior radiation therapy, with those who have received pelvic/abdominal radiation at greater risk
- History of liver disease

More information

This version of your patient’s results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient’s genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient’s biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Simvastatin

Your patient's risk of side effects: **low risk**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene or location</strong></td>
<td><strong>Test SNP</strong></td>
<td><strong>markers</strong></td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>rs4149056</td>
<td>TT</td>
</tr>
</tbody>
</table>

see page 8 for an explanation of this table format

Your patient's results

We looked at one place in your patient's genetic code where a one-letter variation, or SNP, affects your patient's odds of having simvastatin-induced myopathy. This site is located in the SLCO1B1 gene, and is known as the SLCO1B1*5 variant (pronounced “star 5”).

The table above shows your patient's results, and your patient's genetic markers are TT. What this means for your patient is that, based on these markers, your patient is likely to have a low risk of simvastatin myopathy side effects. Specifically, your patient has no copies of the risk variant “C,” where C confers risk.

Side effects include statin-induced myopathy and rhabdomyolysis after taking this drug.

As stated in one key study: “Overall, the rates of severe myotoxicity with all statins are low, especially with low-to-moderate doses. However, recent trials for those using simvastatin 80 mg daily suggest a higher incidence of myotoxicity compared with maximum approved doses of other statins. Practitioners should be aware of these possible risks and individualize therapy to limit myotoxicity.” ([Ann Pharmacother 2009;43:2012-20](http://www.theannals.com/cgi/content/abstract/43/12/2012))

It is also important to note that these genetic results apply most directly to simvastatin. While the genetic variant covered by this test has also been linked to varying risks for other types of statins, this link is less proven, and Navigenics is not directly applying this genetic result to statins other than simvastatin at this time.

Drug details

**Brand names:** Lipex®, Simcard®, Simlup®, Simvacor®, Vytorin®, Zocor®

**Primary uses:** Simvastatin is used to lower cholesterol and to help prevent heart attack, stroke, and other cardiac events.

The genetics of simvastatin side effects

Navigenics tests for a single genetic variant in the SLCO1B1 gene (known as SLCO1B1*5). SLCO1B1, formerly known by several other names including organic anion transporter 2 (OATP2), OATPC, OATP1B1, liver-specific transporter 1 (LST1), and SLC21A6, is located on chromosome 12. This genetic variant increases the risk of simvastatin-induced myopathy. It is also important to note that these genetic results apply most directly to simvastatin. While the genetic variant covered by this test has also been linked to varying risks for other types of statins, this link is less proven by scientific research, and Navigenics is not directly applying this genetic result to statins other than simvastatin at this time.

Although the mechanism underlying simvastatin-induced myopathy is unclear, it appears to be related to statin concentrations in the blood. Any factor that raises statin concentrations in the bloodstream has the potential to increase the risk of statin-induced myopathy. SLCO1B1 codes for a protein called OATP1B1, which mediates the uptake of various drugs in the liver, including most statins and statin acids. To learn more about the biological pathway of statins, please read the review at www.pharmgkb.org/search/pathway/statin/als-pk.jsp.

Studies suggest that people with the SLCO1B1 genetic risk variant have higher levels of statin in their blood. Among people who carry two copies of the SLCO1B1 risk variant taking 80 mg of simvastatin daily, the five-year risk of myopathy is 18 percent. However, more than half of cases in this trial occurred in first year of treatment. For those with one copy of the SLCO1B1 risk-related variant taking 80 mg of simvastatin daily, the five-year risk of myopathy is three percent. By not prescribing simvastatin to those with one or two copies of the SLCO1B1 risk-related variant (C), the risk of myopathy can be reduced by 60 percent.
Other genetic factors, which Navigenics does not test for, may also increase the risk of statin-induced myopathy.

Clinical notes

As yet, professional organizations have not set guidelines on how physicians should incorporate genetic information into clinical decision-making for this drug. The following suggestions represent current clinical understanding and practices:

Personalized treatment

Because your patient’s genetic results indicate that he/she is at low risk for side effects, you may want to tailor his/her therapy to maximize the effectiveness of statins. Possible treatment options include:

- **Be aware of risks involved with concomitant use of other drugs.** Drugs that carry such risks include fibrates, cyclosporine and amiodarone.
- **Modify your patient’s dose.** Since your patient is at low risk of side effects, you may want to prescribe a higher dose of statins, as appropriate. Lower doses of statins may decrease your patient’s risk of simvastatin-induced myopathy, but may not be as effective in reducing his/her risk of vascular events. These genetic test results may be used to help strike a balance between efficacy and safety. For further details, please see the tables below, which are based on SEARCH. N Engl J Med 359:789. 2008.

### Risk of statin-induced myopathy: Dose matters

<table>
<thead>
<tr>
<th>Dose</th>
<th>Odds ratio</th>
<th>95 percent confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg simvastatin/day (per allele)</td>
<td>2.6</td>
<td>1.3, 5.0</td>
</tr>
<tr>
<td>80 mg simvastatin/day (per allele)</td>
<td>4.5</td>
<td>2.6, 7.7</td>
</tr>
</tbody>
</table>

### Risk of statin-induced myopathy at 80 mg simvastatin/day: Number of risk variants matters

<table>
<thead>
<tr>
<th>Variants (C confers risk)</th>
<th>Odds ratio</th>
<th>95 percent confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT vs. TT</td>
<td>5.0</td>
<td>2.4, 10.2</td>
</tr>
<tr>
<td>CC vs. TT</td>
<td>16.9</td>
<td>4.7, 61.1</td>
</tr>
</tbody>
</table>

Other risk factors

Certain patient health status risk factors may also affect your patient’s risk of side effects, including:

- Dose (risk increases with dose)
- Age (risk increases with age)
- Presence of other diseases, such as diabetes, hypothyroidism, or kidney or liver diseases. The risk of statin-induced rhabdomyolysis may also be increased by unusual strenuous muscular activity.

More information

This version of your patient’s results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient’s genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient’s biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Statins

How effective for your patient: typical effectiveness

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location 1</td>
<td>Test SNP 2</td>
</tr>
<tr>
<td></td>
<td>Patient's markers 3</td>
</tr>
<tr>
<td>APOE</td>
<td>rs429358</td>
</tr>
<tr>
<td></td>
<td>rs7412</td>
</tr>
</tbody>
</table>

Your patient's results

We looked at two places in your patient's genetic code where a one-letter variation, called a SNP, affects your patient's response to simvastatin and pravastatin. The table above shows your patient's results, and your genetic markers include no copies of the risk-related marker "E4." What this means for your patient is that, based on these markers, simvastatin and pravastatin are likely to have typical effectiveness in terms of lowering cholesterol levels and preventing cardiovascular events.

People who carry any combination of the "E2" or "E3" markers, and do not carry any copies of the "E4" marker, like your patient, are more likely to find that use of simvastatin and pravastatin will reduce cholesterol levels as expected. This cholesterol lowering, in turn, is likely to reduce your patient's risk of experiencing serious cardiac events.

Drug details

Brand names: Lipex®, Pravachol®, Vytorin®, Zocor®

Primary uses: Common primary uses include cholesterol reduction and prevention of myocardial infarction, stroke, and other cardiac events.

The genetics of statin effectiveness

The APOE (Apolipoprotein E) gene, located on chromosome 19, codes for a protein that binds to and transports fatty substances, including cholesterol, in the body. APOE comes in three different variations: APOE-2, APOE-3 and APOE-4. Individuals who carry the APOE-4 variant tend to have higher levels of LDL cholesterol and a higher risk of both cardiovascular disease and Alzheimer's disease.

Several studies have shown that individuals who carry the APOE-4 allele don't experience as much of a reduction in LDL level as would be expected after statin treatment. Therefore, APOE-4 carriers are considered less responsive to statin treatment. However, rigorous randomized controlled studies indicate that APOE-4 carriers receiving regular simvastatin or pravastatin treatment actually have improved survival and improved heart attack outcomes over those APOE-4 carriers who do not take a statin. In other words, in the group originally thought to have the poorer cardiovascular prognosis because of their genetics, statin treatment appears to mitigate the excess risk.

APOE-4, therefore, appears to have dual effects, especially when it comes to simvastatin and pravastatin. This variant identifies a group of patients that is both at a higher risk of cardiovascular problems and at the same time more likely to benefit in terms of MI survival rates. This effect appears to be independent of cholesterol lowering, but rather may be due to these statins' other properties, such as their ability to reduce inflammation and CHD risk factors.

Please note on Lipitor: While some evidence suggests that beyond simvastatin and pravastatin, other types of statins, such as atorvastatin (Lipitor) may also share this APOE-4-related pattern, these other types of statins have not yet been sufficiently investigated in rigorous scientific trials that look at overall health outcomes.

The APOE-4 gene also has a large and well-established link to increased risk of Alzheimer's disease, which is included in your patient's Navigenics results, should your patient have chosen to learn their results for Alzheimer's disease.
Other genes have been studied in relation to statin response, but did not pass the Navigenics scientific selection process and are not included at this time. These genes include KIF6, CETP, LIPC, CYP3A5, HMGCoA, and ABCB1.

**Clinical notes**

Professional organizations have yet to set guidelines on how physicians should incorporate genetic information into clinical decision-making on these drugs. The following suggestions represent current clinical understanding and practices to date:

**Treatment considerations**

People with your patient's genetic profile, or genotype, are more likely to have low cholesterol and lower rates of coronary heart disease. Statins tend to lower cholesterol in people with your patient's genotype. However, these medications are less likely to lower your patient's risk of dying after heart attack as much as they do in people of other genotypes.

You may want to consider integrating your patient's genetic profile information into your medication decisions when considering other drugs which may also be effective for reducing the risk of a first or repeat cardiac event.

**More information**

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Succinylcholine

Your patient's risk of side effects: **low risk**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>Scientific name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location 1</td>
<td>Test SNP 2</td>
<td>Patient's markers 3</td>
<td></td>
</tr>
<tr>
<td>BCHE</td>
<td>rs1799807</td>
<td>TT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs1803274</td>
<td>CT</td>
<td></td>
</tr>
</tbody>
</table>

see page 8 for an explanation of this table format

**Your patient's results**

We looked at two places in your patient's genetic code where one-letter variations, called SNPs, affect your patient's odds of having succinylcholine side effects. Both of these variations are in the BCHE gene, and the two variants that can increase the risk of side effects are known as the BCHE A and BCHE K variants.

The table above shows your patient's results, and your patient's genetic markers are TT/CT. What this means for your patient is that, based on these markers, your patient is at low risk of side effects. (See the "Genetics of succinylcholine side effects" section for more details.)

Side effects include a prolonged and potentially life-threatening apnea of respiratory muscles following general anesthesia with succinylcholine or use of the drug during intubation or placement on a ventilator.

**Drug details**

**Brand names:** Anectine®, Quelicin®

**Primary uses:** A skeletal muscle relaxant, administered via IV, used as an adjunct to anesthesia during major surgery or during mechanical ventilation and/or intubation

**The genetics of succinylcholine side effects**

The BCHE gene is named for the protein it regulates, butyrylcholinesterase (BChE), also known as pseudocholinesterase. Variants in the BCHE gene make this protein less effective at breaking down several drugs, including succinylcholine, a skeletal muscle relaxant used during major surgery, ventilation, or intubation.

How much active BChE protein your patient has, and how well that protein works, play a major role in how sensitive your patient is to succinylcholine. About 65 percent of prolonged post-succinylcholine apnea is attributed to BChE protein deficiency, the majority of which is due to BCHE gene variants.

Navigenics tests for the two most common BCHE gene variants, known as BCHE A (rs1799807) and BCHE K (rs1803274). The BCHE K variant is more common than the BCHE A variant, but when the A variant is present, it carries more risk. Other, extremely rare, BCHE gene variants (for which Navigenics does not test) can also raise the risk of prolonged post-succinylcholine apnea. For details on these variants, contact a Navigenics Genetic Counselor by calling the number at the top of this page.

**Clinical notes**

Professional organizations have yet to set guidelines on how physicians should incorporate genetic information into clinical decision-making on this drug. The following suggestions represent current clinical understanding and practices to date. You and the rest of your patient's clinical team may want to evaluate your patient's results in the context of his/her complete health picture when making medication decisions.

**Factors influencing your patient's side effects profile**

The BCHE A and K variants, located on chromosome 3q26, are two predictors of adverse succinylcholine reaction. Other rare genetic BCHE risk variants also exist and are not covered by the Navigenics test. A negative BCHE A/K genotype does not guarantee that such side effects will not occur.
Some medications may interact with succinylcholine and increase a person's risk of side effects, such as:

- Some inhaled anesthetics, such as isoflurane and desflurane
- Local anesthetics, such as lidocaine
- Calcium channel blockers, such as benidipine and manidipine
- Antiarrhythmics, such as procainamide
- Non-penicillin antibiotics
- Immunosuppressants, such as glucocorticoids
- Antipsychotics, such as promazine and lithium

These health status factors also affect a person's risk of side effects:

- Kidney or liver impairment
- Electrolyte imbalance
- Sensitivity to muscle relaxants
- Malnutrition
- Being female
- Pregnancy
- Chronic oral contraceptive use
- Radiation therapy
- Burns

Other medications to note

Preliminary research has shown that the ways a person reacts to certain other drugs are also affected by the same genetic factors that affect succinylcholine. These drugs include:

- Irinotecan, a cancer medication
- Dibucaine, an anesthetic
- Rivastigamine, a medication used to treat Alzheimer’s disease and other forms of dementia
- Cocaine, most commonly known as an illegal narcotic but also sometimes prescribed legally as an anesthetic

Research on genetic factors and these drugs is more preliminary than it is for succinylcholine. If you have any questions about your patient's genetic results and any of these drugs, please contact a Navigenics Genetic Counselor by calling the phone number at the top of this page.

Additional testing

Consider standard protein (serum cholinesterase) testing to assess your patient's BCHE status in vitro before procedures requiring succinylcholine. Learn more about this type of testing > (www.nlm.nih.gov/medlineplus/ency/article/003358.htm)

Treatment considerations

Since your patient's genetic results indicate that he/she is at low risk, you may not want to consider alternate therapies or procedures to prevent post-succinylcholine apnea.

More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
- An overview of all the possible genetic combinations related to this side effect.
- Information on implications for your patient's biological relatives.
If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.
Thiopurines

Your patient's risk of side effects: **low risk**

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Patient's results</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location</td>
<td>Test SNP</td>
<td>Patient's markers</td>
</tr>
<tr>
<td>TPMT</td>
<td>rs1142345</td>
<td>TT</td>
</tr>
<tr>
<td></td>
<td>rs1800460</td>
<td>CC</td>
</tr>
<tr>
<td></td>
<td>rs1800462</td>
<td>CC</td>
</tr>
</tbody>
</table>

**Note for those at moderate risk of side effects:** Because the TPMT*3A variant contains the variations found in the TPMT*3B and TPMT*3C variants, this assay cannot distinguish the TPMT*1/TPMT*3A genotype (moderate risk) from the TPMT*3B/TPMT*3C genotype (high risk). However, the TPMT*3B/TPMT*3C genotype is extremely rare in the United States. If these results show the TPMT*1/TPMT*3A genotype, you may want to consider follow-up testing using sequencing methods.

Your patient's results

We looked at three places in your patient's genetic code where one-letter variations, or SNPs, affect your patient's odds of serious bone marrow suppression after treatment with either AZA or 6-MP. These SNPs are located in the TPMT (thiopurine S-methyltransferase) gene.

The table above shows your patient's results, and your patient's markers are *1/*1 (pronounced "star one/star one"). What this means for your patient is that, based on the markers Navigenics tested, your patient is likely to have a low risk of side effects. Specifically, your patient has none of the genetic markers we tested for that cause reduced protein activity.

Side effects include severe myelotoxicity.

However, other variants which may increase the risk of side effects do exist, and are not currently covered by this test result. Therefore, you may still want to consider TPMT enzyme testing or additional genetic testing before placing your patient on AZA or 6-MP.

**Please note:** These results apply to two thiopurine drugs, azathioprine and 6-Mercaptopurine. This class of drugs also includes one additional thiopurine, called 6-TG, which is not included in this genetic result.

Drug details

**Brand names:** Azasan®, Imuran®, Purinethol®

**Primary use:** AZA and 6-MP are approved by the FDA for treatment of inflammatory bowel disease, rheumatoid arthritis, certain types of cancer, dermatological conditions and to prevent tissue rejection after organ transplantation.

**Secondary use:** AZA and 6-MP can also be used to treat multiple sclerosis.

The genetics of thiopurine side effects

The TPMT gene, located on chromosome 6, is named for the enzyme it produces, Thiopurine S-methyltransferase. Variants in the TPMT gene make this enzyme less effective at breaking down thiopurine drugs such as azathioprine (AZA) and 6-Mercaptopurine (6-MP), which are used to treat a variety of conditions, including autoimmune conditions and cancer.

How much TPMT enzyme a person has, and how well that enzyme functions, plays a big part in how likely a person is to experience bone marrow toxicity after AZA or 6-MP therapy. Inheriting a single copy of a non-functional TPMT variant results in "intermediate" TPMT activity, whereas people who inherit two copies of these variants are said to have "low or absent" TPMT activity.
To date, 22 variants in the TPMT gene have been described. Navigenics tests for three SNPs that allow us to determine the four most common versions of the TPMT gene associated with reduced levels of enzyme activity - TPMT*2, TPMT*3A, TPMT*3B, and TPMT*3C - which account for 80 to 95 percent of individuals with decreased or absent TPMT enzyme activity.

Non-functional TPMT variants are more common among African Americans and Caucasians than in Asians.

Other rare TPMT variants (for which Navigenics does not test) can also raise a person’s risk for bone marrow toxicity after AZA or 6-MP therapy. See a detailed overview of rare TPMT variants > (www.pharmgkb.org/search/annotatedGene/tpmt/variant.jsp)

Clinical notes

The FDA recommends that “consideration be given to either genotype or phenotype patients for TPMT” before prescribing AZA or 6-MP. Treatment strategy may be adjusted based on both genotype and phenotype results.

The following suggestions represent current clinical understanding and practices to date:

Follow-up testing

Although your patient does not carry the non-functional variants included in this test, you may want to order follow-up testing to better understand how your patient’s genetic makeup affects his/her response to AZA or 6-MP. Follow-up options may include TPMT enzyme levels or additional TPMT gene testing for rare variants. TPMT enzyme activity is clinically available.

Personalized treatment

AZA or 6-MP may be a good choice for your patient, depending on other factors such as active TPMT enzyme levels. Please note that TPMT testing cannot substitute for routine complete blood count (CBC) monitoring in patients receiving AZA or 6-MP.

Other risk factors

• Possible drug-drug interactions: Bone marrow suppression due to AZA or 6-MP treatment may be exacerbated by co-administration of drugs that inhibit TPMT, such as the anti-inflammatory drugs olsalazine, mesalazine, or sulphasalazine.

More information

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• Details on the science behind these results.
• A look at how your patient's genetic profile for this side effect compares to that of other people of the same ancestry.
• An overview of all the possible genetic combinations related to this side effect.
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Warfarin

How effective for your patient: likely to require customized dose

<table>
<thead>
<tr>
<th>What we looked for</th>
<th>Test SNP</th>
<th>Patient’s results</th>
<th>Scientific name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene or location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>rs1057910</td>
<td>AA</td>
<td>&quot;1/2&quot;</td>
</tr>
<tr>
<td></td>
<td>rs1799853</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td>VKORC1</td>
<td>rs9923231</td>
<td>CC</td>
<td>&quot;1/2&quot;</td>
</tr>
<tr>
<td>CYP4F2</td>
<td>rs2108622</td>
<td>CT</td>
<td>&quot;1/3&quot;</td>
</tr>
</tbody>
</table>

WarfarinDosing.org input for your genotype:

VKORC1 - 1639/3673
Genotype = GG
CYP4F2 V433M
Genotype = CT

Please note: Other genetic variants included in the WarfarinDosing.org calculator are not included in these results, as their significance has not been sufficiently determined. These include GGCX rs11676382, CYP2C9*5, and CYP2C9*6. Calculator fields for these variants should be marked unavailable.

Your patient's results

We looked at four places in three genes in your patient’s genetic code where a one-letter difference, also called a genetic marker or SNP, affects his or her optimum warfarin dosage. We then evaluated your patient’s warfarin dosing requirements based on his or her genetic makeup, or genotype. The table above summarizes your patient’s genetic results. Your patient's results indicate that he or she carries at least one marker in the CYP2C9 or VKORC1 genes that makes him or her likely to require a customized warfarin dose.

PLEASE NOTE: Your patient’s genetic results are provided in two formats – one preferred by Navigenics and many other genetic testing providers, and one preferred by www.WarfarinDosing.org, a dosing calculation tool for clinicians. If you choose to use the WarfarinDosing.org calculator, please use the WarfarinDosing.org version of your patient's results when entering patient data into the calculation tool.

These differences in formats reflect only preferences in the way genetic data can be reported, and do not make the results provided by Navigenics any less accurate.

Drug details

Brand names: Coumadin®, Jantoven®, Marevan®, Lawarin®, Waran®

Primary uses: Warfarin is prescribed to prevent clotting in a variety of conditions including atrial fibrillation, deep vein thrombosis, pulmonary embolism, presence of artificial heart valves, antiphospholipid syndrome and, occasionally, after heart attacks.

The genetics of warfarin sensitivity

The genetics of warfarin are complex, as are the challenges of personalized warfarin dosing. In analyzing your patient’s warfarin-related genetics, Navigenics looks at four places contained within three genes in your patient's genetic code – CYP2C9, CYP4F2, and VKORC1.

The cytochrome P450 family of proteins, called CYP (pronounced “sip”), are the major proteins involved in breaking down and activating important ingredients in various drugs, including warfarin. Navigenics tests for three SNPs related to two CYP proteins – two SNPs in a gene called CYP2C9, and one SNP in a gene called CYP4F2.

In the CYP2C9 gene, two variants – called *2 and *3 (pronounced “star 2” and “star 3”) — can slow down the body's ability...
to break down warfarin, resulting in a higher, more prolonged concentration of the drug in the bloodstream. People who carry these variants need a lower initial dose of warfarin. These well-researched gene variants are estimated to account for 17 percent of the variance in warfarin dose. A single copy of the T variant at a SNP called rs1799853 indicates one copy of CYP2C9*2, and two copies is noted as CYP2C9*2/*2. A single copy of the C variant at a SNP called rs1057910 indicates a copy of CYP2C9*3, and two copies is noted as CYP2C9*3/*3. In this test, having no copies of either of these variants is considered the normal functioning version, which is called CYP2C9*1 (pronounced “star 1”). It is also important to note that occasionally other variants may affect CYP2C9 function. These rarer variants will not be detected by this test.

The importance of the CYP4F2 gene in warfarin metabolism has only recently been established. This gene is estimated to account for one to two percent of warfarin dosing variability. In the CYP4F2 gene, the T variant at a SNP called rs2108622, also called the *3 variant, appears to decrease the function of the protein, causing people with one or two copies of the variant to require slightly higher doses of warfarin. Similarly, the absence of a *3 variant, in this test, is considered to be a normally functioning version and is called CYP4F2*1.

The Vitamin K epoxide reductase (VKORC1) gene is involved in vitamin K recycling and accounts for up to 23 percent of the variance in warfarin dosing. Clots require Vitamin K to form, and warfarin prevents clotting by inhibiting the function of VKORC1, thereby reducing the body's Vitamin K levels. The Navigenics test includes one SNP variant in the VKORC1 gene, called rs9923231, or -1639. People with two copies of the T variant at this SNP require a lower dose and those with two copies of a C variant require a higher dose of warfarin for optimal outcome. The rs9923231 SNP is an excellent predictor of warfarin dose in most people. However, other SNPs in the VKORC1 gene may also influence your patient's risk, particularly in people of African descent.

Other genetic variants that have been less conclusively linked to warfarin dosing include GGCX rs11676382, CYP2C9*5, and CYP2C9*6. These variants are not included in your patient's results, as their significance has not been sufficiently determined.

**Clinical notes**

The FDA recommends that VKORC1 and CYP2C9 gene variants, which are included in this test result, be used to optimize warfarin dosing (www.pharmgkb.org/clinical/warfarin.jsp). The following suggestions represent current clinical understanding and practices to date.

**Follow-up testing**

It's possible that you may want to order additional testing to better understand how your patient's genetic makeup affects his/her response to warfarin, especially if your patient is not of Caucasian ancestry. For example, rarer variants have been identified in CYP2C9 and, for patients of African ancestry, other SNPs in the VKORC1 gene may also influence optimal warfarin dosing. For more information on additional testing, contact a Navigenics Genetic Counselor.

**Dosing calculators**

You may want to enter your patient's genetic information into a dosing calculator, along with other clinical risk factors, to determine the proper dose for your patient. One option is www.WarfarinDosing.org, a dosing calculation tool for clinicians.

**PLEASE NOTE:** Your patient's genetic results are provided in two formats above – one preferred by Navigenics and many other genetic testing providers, and one preferred by WarfarinDosing.org. If you choose to use the WarfarinDosing.org calculator, please use that version of your patient's results when entering patient data into the calculation tool.

**Other risk factors**

Factors beyond your patient's genetic markers can also affect his/her optimal dose of warfarin. These include:

- Age
- Gender
- Weight
- Diet
Other drugs, such as certain antibiotics, anti-inflammatories, and statins

Personalized treatment

If your patient requires warfarin therapy, you may want to tailor his/her therapy to optimize treatment. Possible treatment options include:

- **Modifying dose.** You can use your patient’s genetic results to help reach the proper INR range for your patient more quickly and strike a balance between efficacy and safety.
- **Watching for drug-drug interactions.** Be aware of risks involved with concomitant use of other drugs (such as certain antibiotics and statins) and herbs (such as ginseng).
- **Watching for diet-drug interactions.** Be aware of risks involved with certain foods (such as those high in vitamin K) and alcohol.

Overview: warfarin-related genetic markers

These three tables illustrate how the genetic variations (SNPs) tested for warfarin sensitivity combine to indicate a person’s warfarin-related genetic profile.

Specifically, we look at two places in the CYP2C9 gene where certain variants indicate that a person is likely to require a reduced warfarin dose. One or two C variants in the rs1057910 SNP (otherwise known as *3) or T variants in the rs1799853 SNP (otherwise known as *2) indicate that a person is likely to require a reduced warfarin dose.

Additionally, we look at one place in the VKORC1 gene, where a CT genotype indicates that a person is likely to require a standard dose, a TT genotype indicates that a person is likely to require a reduced dose, and a CC genotype indicates that a person is likely to require an increased warfarin dose.

Finally, we look at one place in the CYP4F2 gene, which has a smaller, but still clinically significant, effect on warfarin dose. One or two T variants in this gene indicate that a person may require an increased warfarin dose.

### Table 1. Warfarin dosing (CYP2C9)

<table>
<thead>
<tr>
<th>Gene: CYP2C9</th>
<th>SNP: rs1057910 risk marker= T</th>
<th>SNP: rs1799853 risk marker= C</th>
<th>Scientific Name</th>
<th>Genotype Frequency in Reference Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>African</td>
</tr>
<tr>
<td>CC</td>
<td>AA</td>
<td>*1/*1</td>
<td>standard dose</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CC</td>
<td>CC</td>
<td>*1/*3</td>
<td>reduced dose</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CC</td>
<td>CC</td>
<td>*3/*3</td>
<td>reduced dose</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CT</td>
<td>AA</td>
<td>*1/*2</td>
<td>reduced dose</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CT</td>
<td>AC</td>
<td>*2/*3</td>
<td>reduced dose</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>TT</td>
<td>AA</td>
<td>*2/*2</td>
<td>reduced dose</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

N/A= not available

Genotype combination frequencies not shown here have not been described in the scientific literature.

### Table 2. Warfarin Dosing (VKORC1)
Table 3. Warfarin Dosing (CYP4F2)

<table>
<thead>
<tr>
<th>Gene: CYP4F2</th>
<th>SNP: rs2108622</th>
<th>What it means</th>
<th>Genotype Frequency in Reference Population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Scientific Name</td>
<td></td>
<td>African</td>
</tr>
<tr>
<td>CC</td>
<td>*1/*1</td>
<td>standard dose</td>
<td>76%</td>
</tr>
<tr>
<td>CT</td>
<td>*1/*3</td>
<td>increased dose</td>
<td>23%</td>
</tr>
<tr>
<td>TT</td>
<td>*3/*3</td>
<td>increased dose</td>
<td>2%</td>
</tr>
</tbody>
</table>

More information

This version of your patient's results represents an abridged version of the full results they received. If you wish to see more information, ask your patient to provide their complete results, which include:

- Details on the science behind these results.
- Information on implications for your patient's biological relatives.

If you have questions, please contact a Navigenics Genetic Counselor by calling the phone number displayed at the top of this page.