Report Contents

1. Coriell Personalized Medicine Collaborative Research Study Report. This report includes all data included in the clinical report as well as supplemental interpretations and educational material. This research report is based on Questionnaires Finalized on 08/01/2010

2. Clinical Report. This report was generated and approved by Coriell's CLIA certified genotyping laboratory.
CPMC Research Study Report

Name: STEVE CPMC  Gender: Male
Date of Birth:  Date Collected: 11-30-2016
Coriell ID: DEMOSTEVE  Date Received: 11-30-2016
Lab Accessioning Number: DEMOSTEVE  Date of Report: 07-21-2014
Ordering Physician: Dr. Edward Viner

Risk of Developing An Intracranial Aneurysm Based on:

- CPMC Intracranial Aneurysm Variants
  - rs6841581
  - rs9298506
  - rs9315204
  - rs12413409
- Family History
- Smoking
- Hypertension (high blood pressure)

The CPMC is a research study investigating the utility of personalized genomic information on health and health behavior. Most common health conditions are caused by an interaction between multiple genetic variants and non-genetic risk factors such as lifestyle and environment. The genetic variant risk in this report is based on four genetic variants, but does not represent your complete genetic risk for developing an intracranial aneurysm. These results were generated as part of this research study in a CLIA-approved laboratory.

More information about the study, how to interpret CPMC results, and how we calculate risk is available on our website http://cpmc.coriell.org or by contacting our genetic counselor. Participants may schedule an appointment with our board-certified genetic counselor through the web portal by clicking on "request an appointment". Our genetic counselor also can be reached by email at cpmcgc@coriell.org or by phone at 888-580-8028.

This research report includes all data included in the clinical report as well as supplemental interpretations and educational material. Please see the report that follows for the official clinical report.
Risk factors may be related to each other and risk estimates cannot be combined. This graph provides a summary of the relative risk for 4 genetic variants, family history, smoking, and high blood pressure.

An estimated 3 in 100 individuals have an unruptured intracranial aneurysm.

<table>
<thead>
<tr>
<th>Chart Color</th>
<th>Relative Risk Due To:</th>
<th>Minimum Risk</th>
<th>Maximum Risk</th>
<th>Your Risk</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Variants</td>
<td>0.31</td>
<td>1.50</td>
<td>1.30</td>
<td>Based on your combination of genetic variants, you are 30% more likely (or 1.3 times as likely) to develop an intracranial aneurysm than an average individual.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Having this combination of genetic variants increases your risk of developing an intracranial aneurysm.</td>
</tr>
<tr>
<td>Family History</td>
<td>1.00</td>
<td>4.00</td>
<td>4.00</td>
<td>Based on your family history, you are 4.00 times more likely to develop an intracranial aneurysm compared to someone who does not have a first degree relative with an intracranial aneurysm.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Having a parent, sibling, or child with an intracranial aneurysm contributes to your risk of developing an intracranial aneurysm.</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>1.00</td>
<td>2.20</td>
<td>2.20</td>
<td>Because you are a current smoker you are 2.20 times more likely to develop an intracranial aneurysm compared to never smokers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Being a current smoker contributes to your risk of an intracranial aneurysm.</td>
</tr>
<tr>
<td>Chart Color</td>
<td>Relative Risk Due To:</td>
<td>Minimum Risk</td>
<td>Maximum Risk</td>
<td>Your Risk</td>
<td>Interpretation</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>High Blood Pressure</td>
<td>1.00</td>
<td>2.30</td>
<td>2.30</td>
<td>Because you reported that you have high blood pressure, you are 2.30 times as likely to develop intracranial aneurysm as individuals who do not have high blood pressure.</td>
</tr>
</tbody>
</table>

*Having high blood pressure contributes to your risk of intracranial aneurysm.*
Intracranial Aneurysm (Multi-variant Version #1)

The table and picture below show how many individuals will fall into each of the genetic risk categories for intracranial aneurysm based on 4 genetic variants.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Risk</td>
<td>14 in 100 people</td>
</tr>
<tr>
<td>Average Risk</td>
<td>72 in 100 people</td>
</tr>
<tr>
<td>Elevated Risk</td>
<td>14 in 100 people</td>
</tr>
</tbody>
</table>
Intracranial Aneurysm
Multi-variant Genetic Risk

The CPMC tested 4 sites of genetic variation in 4 genes associated with intracranial aneurysm. Your result for each genetic variant tested is shown below in yellow.

<table>
<thead>
<tr>
<th>Variants Tested</th>
<th>Reference Value</th>
<th>Your Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6841581</td>
<td>CC</td>
<td>CC</td>
</tr>
<tr>
<td>rs9298506</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>rs9315204</td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>rs12413409</td>
<td>CC</td>
<td>CC</td>
</tr>
</tbody>
</table>
Based on your combination of genetic variants, you are 30% more likely (or 1.3 times as likely) to develop an intracranial aneurysm than an average individual.

Having this combination of genetic variants increases your risk of developing an intracranial aneurysm.

The CPMC tested 4 sites of genetic variation in or near 4 genes associated with intracranial aneurysm.

Your risk due to the genetic variants tested was estimated and compared to the genetic risk of an average individual.

Other genetic variants, not currently included in this CPMC test, may also influence your risk to develop an intracranial aneurysm.

These results are based on multiple studies.
Intracranial Aneurysm
Risk Due To Family History
You reported that a first degree relative (parent, sibling or child) has had an intracranial aneurysm.

<table>
<thead>
<tr>
<th>Chart Color</th>
<th>Minimum Risk</th>
<th>Maximum Risk</th>
<th>Your Risk</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>4.00</td>
<td>4.00</td>
<td>Based on your family history, you are 4.00 times more likely to develop an intracranial aneurysm compared to someone who does not have a first degree relative with an intracranial aneurysm.</td>
</tr>
</tbody>
</table>

*Having a parent, sibling, or child with an intracranial aneurysm contributes to your risk of developing an intracranial aneurysm.*

Risk is compared based on family history.

People with a first degree relative with an intracranial aneurysm were compared to people with no family history of intracranial aneurysm to determine relative risk of developing an intracranial aneurysm.

A relative risk greater than 1.00 indicates an increased risk.

These results are based on multiple studies.
Intracranial Aneurysm
Risk Due To Smoking Status
You reported that you are a current smoker.

<table>
<thead>
<tr>
<th>Chart Color</th>
<th>Minimum Risk</th>
<th>Maximum Risk</th>
<th>Your Risk</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>2.20</td>
<td>2.20</td>
<td>Because you are a current smoker you are 2.20 times more likely to develop an intracranial aneurysm compared to never smokers.</td>
</tr>
</tbody>
</table>

Being a current smoker contributes to your risk of an intracranial aneurysm.

Risk is compared based on smoking habits.

Current and former smokers were compared to people who have never smoked to determine relative risk.

A relative risk of greater than 1.00 indicates an increased risk.

These results are based on multiple studies.
**Intracranial Aneurysm**

**Risk Due To High Blood Pressure**

You reported that you have high blood pressure.

<table>
<thead>
<tr>
<th>Chart Color</th>
<th>Minimum Risk</th>
<th>Maximum Risk</th>
<th>Your Risk</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>2.30</td>
<td>2.30</td>
<td>Because you reported that you have high blood pressure, you are 2.30 times as likely to develop intracranial aneurysm as individuals who do not have high blood pressure.</td>
</tr>
</tbody>
</table>

*Having high blood pressure contributes to your risk of intracranial aneurysm.*

Risk is compared based on diagnosis of high blood pressure.

Men who have high blood pressure are compared to men who do not have high blood pressure to determine relative risk.

A relative risk greater than 1.00 indicates an increased risk.

These results are based on multiple studies.
Intracranial Aneurysm (Multi-variant Version #1)

We all have 2 copies of every gene, one inherited from each of our parents. Each copy may have small changes called genetic variants. Some genetic variants are associated with an increased risk of developing a disease. Some genetic variants are associated with a decreased risk of developing a disease.

The CPMC tested 4 sites of genetic variation in or near 4 genes associated with intracranial aneurysm. Background information about each genetic variant tested is shown below.

<table>
<thead>
<tr>
<th>Genetic Variants</th>
<th>Variant Type</th>
<th>Gene</th>
<th>Chromosomal Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6841581</td>
<td>C=non-protective</td>
<td>Upstream of EDNRA</td>
<td>4q31.22</td>
</tr>
<tr>
<td></td>
<td>T=protective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9298506</td>
<td>A=non-protective</td>
<td>Intergenic</td>
<td>8q11.23</td>
</tr>
<tr>
<td></td>
<td>G=protective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9315204</td>
<td>C=non-risk</td>
<td>STARD13</td>
<td>13q13.1</td>
</tr>
<tr>
<td></td>
<td>T=risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs12413409</td>
<td>C=non-protective</td>
<td>CNNM2</td>
<td>10q24.32</td>
</tr>
<tr>
<td></td>
<td>T=protective</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Causes

Genetic vs. Non-Genetic Risk Factors

Intracranial aneurysms can be caused by both genetic factors and non-genetic (or environmental) risk factors.

It is estimated that non-genetic factors (like smoking and high blood pressure) account for about 59% of the risk of developing an intracranial aneurysm.

It is estimated that 41% of the risk for developing an intracranial aneurysm is based on genetic risk factors. This estimate accounts for both known and unknown gene variants.

There are many different genetic and non-genetic risk factors that contribute to the risk of developing an intracranial aneurysm. We are only able to tell you about your family history risk, 4 genetic risk factors, and 2 non-genetic risk factors for an intracranial aneurysm.
An estimated 3 in 100 individuals have an unruptured intracranial aneurysm.
Intracranial Aneurysm

- These results alone do NOT diagnose intracranial aneurysm. Intracranial aneurysm must be diagnosed by your health care provider.
- This result does NOT mean that you have or will absolutely develop an intracranial aneurysm.
- This result does NOT mean that you will not develop an intracranial aneurysm in the future.
- This result ONLY assesses your risk for developing an intracranial aneurysm due to the factors presented in this report and does not mean that other genetic variants or risk factors for intracranial aneurysm are present or absent.
- Personal risk factors, such as age, family history or lifestyle, may have a greater impact on your risk to develop an intracranial aneurysm than any individual or multiple genetic variant(s).
- Risk estimates are based on current available scientific literature.
- Although rare, it is possible that you may receive an incorrect result; 100% accuracy of reported results cannot be guaranteed.
- Occasionally there may be a specific variant on a gene chip that is not able to be read or interpreted. In this case you will not receive a result for that variant. It is expected that you will receive results for about 95% of variants approved by the ICOB.
- Our method of estimating genetic risk due to multiple genetic variants requires complete data. If data are missing for any individual genetic variant included in our analysis, we will not be able to provide you a genetic risk estimate.
- Relative risks used to estimate risk of disease for CPMC participants are based on groups of people with the same risk or protective factor as the individual CPMC participant. In some cases, the relative risk is estimated based upon an odds ratio and known or assumed disease prevalence.
- Separate risk estimates for each risk or protective factor have been given. Risk or protective factors may be related to each other and risk estimates cannot be combined.
- Risk information for non-genetic factors is based on information you provided in your medical, family, lifestyle questionnaire. If you did not provide answers or if you answered “do not know”, risk estimates for some factors may not be available.
- Risk information for non-genetic factors is based on information you provided in your medical, family, lifestyle questionnaire and may not be reflective of your current risk if any of these factors have changed. You will be given the opportunity to update your medical, family and lifestyle questionnaire responses periodically.
- Every effort will be made to provide you with risk information based on your reported race/ethnicity. However, data may not be available for all races/ethnicities for all risk factors. Please see your individual results to determine which race/ethnicity the data given is based on.
Methods

Intracranial Aneurysm

This condition and genetic variant(s) were approved by the Informed Cohort Oversight Board (ICOB)

Test Methodology
Saliva samples were collected using Oragene DNA Collection Kits (DNA Genotek) and DNA was extracted manually according to the manufacturer's instructions. Purified DNA was quantified using UV absorbance at 260 nm. Five hundred nanograms of the resulting DNA from each sample were used as template in the Affymetrix Genome-Wide Human SNP Nsp/Sty 6.0 GeneChip assay. Data analysis was performed using Affymetrix Genotyping Console software.

See CPMC Technical Paper for genetic variant selection and reporting methodology.

[Risk interpretation based on Coriell's Intracranial Aneurysm Research Risk Algorithm Version 1 (July 22, 2014)]

### Sample Results

**Clinical Report for Intracranial Aneurysm (Multi-variant)**

<table>
<thead>
<tr>
<th>Gene/Region</th>
<th>Variant Tested</th>
<th>Reference Genotype</th>
<th>Your Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upstream of EDNRA</td>
<td>rs6841581</td>
<td>CC</td>
<td>CC</td>
<td>Without considering other genetic variants, individuals with this result are at a higher risk to develop an intracranial aneurysm compared to someone with one or two copies of the protective variant. These risk estimates are based on studies involving multiple populations that include individuals with Asian and European ancestry.*</td>
</tr>
<tr>
<td>Intergenic</td>
<td>rs9298506</td>
<td>AA</td>
<td>AA</td>
<td>Without considering other genetic variants, individuals with this result are at a higher risk to develop an intracranial aneurysm compared to someone with one or two copies of the protective variant. These risk estimates are based on studies involving multiple populations that include individuals with Asian and European ancestry.*</td>
</tr>
<tr>
<td>STARD13</td>
<td>rs9315204</td>
<td>CC</td>
<td>CT</td>
<td>Without considering other genetic variants, individuals with this result are 19% more likely (or 1.19 times as likely) to develop an intracranial aneurysm as someone with no copies of this variant. These risk estimates are based on studies involving multiple populations that include individuals with Asian and European ancestry.*</td>
</tr>
<tr>
<td>CNNM2</td>
<td>rs12413409</td>
<td>CC</td>
<td>CC</td>
<td>Without considering other genetic variants, individuals with this result are at a higher risk to develop an intracranial aneurysm compared to someone with one or two copies of the protective variant. These risk estimates are based on studies involving multiple populations that include individuals with Asian and European ancestry.*</td>
</tr>
</tbody>
</table>

**Other Risks**

Other genetic variants and other risk factors including co-morbidities, lifestyle and family history may contribute to the risk of intracranial aneurysm. For additional information on other risk factors please see the accompanying CPMC research report.

---

*When race/ethnicity specific risk estimates are not available, risk estimates based on European populations are provided.

**Risk Interpretation based on Coriell's Intracranial Aneurysm Clinical Risk Algorithm Version 1 (July 22, 2014)**

**Test Limitations**

DNA-based testing is highly accurate, however there are many sources of potential error including: mis-identification of samples, rare technical errors, trace contamination of PCR reactions, and rare genetic variants that interfere with analysis. There may be other variants, not included in this test, that influence the risk to develop an intracranial aneurysm. This test is not diagnostic for an intracranial aneurysm and cannot rule out the risk of developing an intracranial aneurysm in the future. Risk estimates are based on current available literature (see references). This test or one or more of its components was developed and its performance characteristics determined by the Coriell Institute for Medical Research. It has not been approved by the Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary. The Coriell Institute is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high-complexity testing.

**Test Methodology**

Saliva samples were collected using Oragene DNA Collection Kits (DNA Genotek) and DNA was extracted manually according to the manufacturer’s instructions or automatically using a DNAAdvance Kit (Agencourt). Purified DNA was quantified using UV absorbance at 260 nm. Five hundred nanograms of the resulting DNA from each sample were used as template in the Affymetrix Genome-Wide Human
SNP Nsp/Sty 6.0 GeneChip assay. Data analysis was performed using Affymetrix Genotyping Console software.

References