Integration of Genomics into Medical Practice

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Disclosures

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Entity</th>
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<tbody>
<tr>
<td>Consultant</td>
<td>Novartis, Alexion, AstraZeneca</td>
</tr>
<tr>
<td>Educational Program</td>
<td>Axis</td>
</tr>
<tr>
<td>Advisory Board</td>
<td>Accolde</td>
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<tr>
<td>Board of Directors</td>
<td>American College of Medical Genetics and Genomics, Children's Tumor Foundation</td>
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<tr>
<td>Advisor</td>
<td>Neurofibromatosis Therapeutic Acceleration Project</td>
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<tr>
<td>Founding Member</td>
<td>Envision Genomics</td>
</tr>
<tr>
<td>Salary</td>
<td>University of Alabama at Birmingham</td>
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When will physicians routinely use genomic medicine in day-to-day practice?

https://en.wikipedia.org/wiki/Hype_cycle

Abby
Seth
Laura
Newborn Screening

Diagnosis

Prenatal Diagnosis

Presymptomatic Testing

Preconceptional Screening

Predispositional Testing

Newborn Screening

Shortly after birth, blood is taken from Laura’s heel and sent to the State Newborn Screening Laboratory. Her parents are told that this is a routine test. No problems are found, and no follow-up is needed.
Genomic Newborn Screening
Newborn Screening

Diagnosis

Preconceptional Screening

Prenatal Diagnosis

Presymptomatic Testing

Predispositional Testing

Diagnostic Testing

Laura is now 3 and her brother Seth is 5. Seth has been experiencing developmental problems, and is diagnosed as having autism.
The Diagnostic Odyssey
Incidental Findings

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

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ACMG Incidental Findings
Recommendations

- Constitutional mutations on minimal list should be reported regardless of age of patient
- Laboratories should seek and report specific types of mutations on list
- Ordering clinician responsible for pre- and post-test counseling
- Patients may opt out of learning about incidental findings

Gene List

<table>
<thead>
<tr>
<th>Type</th>
<th>Genes</th>
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<tr>
<td>Tumor Predisposition</td>
<td>BRCA1, BRCA2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, VHL, MEN1, RET, NTRK1, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1, NF2</td>
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<tr>
<td>Connective Tissue Dysplasia</td>
<td>COL3A1, FBNA1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11</td>
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<tr>
<td>Cardiomyopathy (Hypertrophic, dilated)</td>
<td>MYBPC3, MYH7, TNN1, TNN2, TNN3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LAMA1</td>
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<tr>
<td>Arrhythmia (Arrhythmogenic RVCM, Romano-Ward, Brugada)</td>
<td>RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, KCNH2, SCN5A</td>
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<td>Hypercholesterolemia</td>
<td>LDLR, APOB, PCSK9</td>
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<tr>
<td>Malignant hyperthermia</td>
<td>RYR1, CACNA1S</td>
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Laura is now married. She and her husband are considering starting a family and meet with her obstetrician-gynecologist. They are both of Northern European ancestry and are offered carrier testing for cystic fibrosis.
Genomic Carrier Screening
Newborn Screening

Diagnosis

Preconceptional Screening

Prenatal Diagnosis

Presymptomatic Testing

Predispositional Testing

Laura and her Tom are indeed found to both be cystic fibrosis carriers. They elect to have prenatal diagnosis by amniocentesis at 16 weeks of pregnancy. The fetus is found to be a CF carrier.
Prenatal Diagnosis

- amniocentesis
- chorionic villus biopsy
- preimplantation diagnosis

Next Generation Prenatal Screening
Genomic Prenatal Diagnosis

Newborn Screening

Diagnosis

Preconceptional Screening

Prenatal Diagnosis

Presymptomatic Testing

Predispositional Testing
Laura is now 45. She has just learned that her older sister Abby, age 49, has been diagnosed as having breast cancer. She is concerned about her own risks, given that there is a family history of others with breast cancer.
Breast Cancer Prevention

Cancer Genomes

Normal  Tumor

Sequence

Difference = cancer-specific genetic changes
Everolimus Treatment of Tuberous Sclerosis

Mutation-Guided Treatment of Cystic Fibrosis
Laura is now 60 years old. She has been in good health. She and her husband have heard about the possibility of having genomic testing, and explore the possibilities on the internet.
Direct-to-Consumer Testing

![Direct-to-Consumer Testing Diagram]

Your Genetic Data

Bruce Korf
24.3 out of 100

Average
23.7 out of 100

What does the Qcoss Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Type 2 Diabetes due to gene sets for men with Bruce Korf’s genotype. The 23andMe Qcoss Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Type 2 Diabetes for the genotypes of other people in your account.

The 23andMe Qcoss Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genotypes, environment and lifestyle may also contribute to one’s chances of developing type 2 diabetes.

Genes vs. Environment

The heritability of type 2 diabetes is estimated to be 26%. This means that environmental factors contribute more to differences in risk for this condition than genetic factors. Genetic factors that play a role in type 2 diabetes include both known factors and known factors such as the 90% we describe here. Environmental factors include obesity, gestational diabetes, giving birth to at least one baby weighing nine pounds or more, high blood pressure, abnormal cholesterol levels, physical inactivity, polycystic ovarian syndrome, other clinical conditions associated with insulin resistance, a history of impaired glucose tolerance or impaired fasting glucose, and a history of cardiovascular disease. (Sources)
Pharmacogenetics

<table>
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<tr>
<th>Variant/Allele Name</th>
<th>Genotype</th>
<th>Combination</th>
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<tbody>
<tr>
<td>rs1799675</td>
<td>CC</td>
<td></td>
</tr>
<tr>
<td>rs1057910</td>
<td>AA</td>
<td>CYP2C19 *1/*1, VKORC1 -695C&gt;A G6</td>
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<tr>
<td>rs8050136</td>
<td>CT</td>
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WGS Workflow

When?
- Prenatal
- New
- Adulthood

Where?
- EHR
- Cloud
- Personal Device
- Cell Nucleus
THE PRECISION MEDICINE INITIATIVE
The best way to predict the future is to invent it.

Alan Kay
Computer Scientist