How much more could we explain with genetics?

Using EHRs to find Undiagnosed Patients
Two reasons why we are not using genetics to their full diagnostic potential

1. Too many Variants of Uncertain Significance (VUS)
Too many VUS's

Hereditary cancer panels results (2013-2019)
N=1820

- Normal: 43%
- Pathogenic: 20%
- Uncertain: 37%

Here are the results for different races:

- White (1626):
  - Normal: 46%
  - Pathogenic: 22%
  - Uncertain: 32%

- Black (170):
  - Normal: 39%
  - Pathogenic: 10%
  - Uncertain: 51%

- Asian (24):
  - Normal: 29%
  - Pathogenic: 17%
  - Uncertain: 54%
Two reasons why we are not using genetics to their full diagnostic potential:

1. Too many Variants of Uncertain Significance (VUS)

2. Patients with mild or atypical presentation are not tested
Chief complaint: Extreme weight loss following a low-carb diet (down to 112 lbs at 5' 3")

Symptoms:
- Borderline diabetes
- Nausea, chronic constipation, GI upset
- Chronic cough
- Recurrent bronchitis

"For as long as he can remember, Steven Knapp never felt well."
Cystic fibrosis: The signs were there all along

<table>
<thead>
<tr>
<th>Cystic fibrosis Symptom</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Chronic bronchopulmonary infections</td>
<td>• Allergies</td>
</tr>
<tr>
<td></td>
<td>• Asthma</td>
</tr>
<tr>
<td></td>
<td>• Post-infectious reactive airway disease</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>• IBD</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>• Diet</td>
</tr>
<tr>
<td>(Pancreatic insufficiency)</td>
<td></td>
</tr>
<tr>
<td>Failure to thrive</td>
<td></td>
</tr>
<tr>
<td>No children</td>
<td></td>
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<tr>
<td>(Male infertility?)</td>
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</table>
Making a Cystic Fibrosis diagnosis: Not just for pediatricians anymore

Age of CF diagnosis is increasing!

Driven by Atypical (Non-DF508 homozygous) diagnoses

Bastarache et al | NEJM (letter) 2019
The potential of large cohorts with sequence + EHR data

Patients with rare variant X

Phenotypes from EHR

1. Find patients with rare genetic variant

2. See if they have Mendelian disease using EHR data (may not be diagnosed)
The potential of large cohorts with sequence + EHR data

1. Find patients with who look like they have Mendelian disease
2. See if they have a rare pathogenic variant
What we would like the EHR to be
What the EHR is really like
**MARFAN SYNDROME**

**HEAD & NECK**
*Eyes*
- Retinal detachment
- Iris hypoplasia

**CARDIOVASCULAR**
*Heart*
- Aortic regurgitation

*Vascular*
- Aortic root dilatation
- Aortic dissection

**SKELETAL**
*Limbs*
- Joint hypermobility

**CHEST**
*Ribs, Sternum, Clavicles & Scapulae*
- Pectus excavatum

**RESPIRATORY**
*Lung*
- Pneumothorax

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Pectus excavatum
Joint dislocation
Pneumothorax
Retinal detachment
Aortic aneurysm

*No Marfan symptoms*
You can differentiate individuals diagnosed with Marfan syndrome using only the features of the disease.

Bastarache et al, Science 2018
A vast number of unknowns
109 genes sequenced for 25k
Disparity in variant knowledge

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Interpreted in ClinVar</th>
<th>Not in Clinvar</th>
<th>VUS in ClinVar</th>
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<tbody>
<tr>
<td>Asian</td>
<td>5.0%</td>
<td>33.7%</td>
<td>38.0%</td>
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<tr>
<td>Black</td>
<td>6.8%</td>
<td>30.3%</td>
<td>37.9%</td>
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<tr>
<td>Hispanic</td>
<td>7.8%</td>
<td>22.4%</td>
<td>31.6%</td>
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<tr>
<td>White</td>
<td>12.5%</td>
<td>21.2%</td>
<td>28.3%</td>
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High-throughput *FBN1* readout

**eMERGEseq**

- Pathogenic
  - 25k patients sequenced for 109 genes
  - 9 clinical sites
  - Phenotypes from billing codes only

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<td>Pathogenic</td>
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<td>3.1</td>
<td>4.2</td>
<td>5.9</td>
<td>3.2</td>
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<td>0.1</td>
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<td>3.7</td>
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<td>1.9</td>
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<td>-1</td>
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<tr>
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<td>0.7</td>
<td>1.7</td>
<td>1</td>
<td>-1.4</td>
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<td>0.5</td>
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<td>0</td>
<td>0.1</td>
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<tr>
<td>5.6</td>
<td>0.5</td>
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Variants of Uncertain Significance
PheRS is highly concordant with what is known

- 23k variants tested
- 10% classified
- 99.3% of known path/benign variants classified correctly
- 1,300 VUS's classified
High-throughput readout for PCSK9

Preliminary analysis

Phenotypic Evidence

- Benign
- Path
- Protect

Exonic Changes:
- exon1
- exon2
- exon3
- exon4
- exon5
- exon6
- exon7
- exon8
- exon9
- exon10
- exon11
- exon12
Can we find undiagnosed patients with PheRS?

- **Cough**: 1 in 8, 0.3% diagnosed with CF
- **Chronic sinusitis**: 1 in 28, 1% diagnosed with CF
- **Bacterial pneumonia**: 1 in 82, 4% diagnosed with CF
- **Bronchiectasis**: 1 in 200, 9% diagnosed with CF
- **Combination of all 4**: 50% diagnosed with CF

**Cystic fibrosis**: 1 in 1500
Diagnosing adults with CF
Better late than never

Pneumonia
Pancreatitis
Chronic airway obstruction
Bronchiectasis
Chronic pulmonary heart disease
Diagnosed with Cystic fibrosis

PheRS

59 60 61 62 63
PheRS is elevated before diagnosis.

80% of adults diagnosed with CF at VUMC had PheRS in the 95th percentile before their diagnosis.

Bastarache et al, JAMIA 2018
Acknowledgements