Genomic Medicine Programs of the National Human Genome Research Institute

Teri Manolio, M.D., Ph.D.

Integrating Genomics into Personalised Healthcare: A Science-for-Policy Perspective

February 13, 2019
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Integrating Genomics into Personalised Healthcare: *TBD*

- From our experience, "where to go next"
- Where do we see the future going, what are the bottlenecks?
- Most important items to assure the power of genomics is translated into the healthcare system for the benefit of the patient?
- Inspire, motivate, perhaps even point to concrete follow-up initiatives
Integrating Genomics into Personalised Healthcare: TBD

- From our experience, "where to go next"
- Where do we see the future going, what are the bottlenecks?
- Most important items to assure the power of genomics is translated into the healthcare system for the benefit of the patient?
- Inspire, motivate, perhaps even point to concrete follow-up initiatives

“The vision thing.”
Integrating Genomics into Personalised Healthcare

- Opportunities
- Obstacles
- Resources
- Collaborations
Integrating Genomics into Personalised Healthcare

• Opportunities
  • Pharmacogenomics
  • Undiagnosed diseases, critically ill newborns
  • Tumor sequencing
  • Germline risk prediction
  • Implementation research
  • Capturing evidence

• Obstacles
• Resources
• Collaborations
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Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)
A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen \( HLA-B^*1502 \), and Cw*0801, A*1101 and DRB1*1202 within the \( HLA \) region occurred at increased frequency in CBZ–SJS patients relative to the controls (Table 1). In particular, \( HLA-B^*1502 \) was present in 100% (44/44) of CBZ–SJS patients but in only 3% (3/101) of CBZ-tolerant patients and in 8.6% (8/93) of the general population.

When the CBZ-tolerant group is used as the control, the presence of \( B^*1502 \) has a 93.6% positive-prediction value for CBZ–SJS, whereas its absence has a negative-prediction value of 100%. In a test for CBZ–SJS, the \( HLA-B^*1502 \) allele should therefore have 100% sensitivity and 97% specificity.
SJS/TEN, **HLA-B*15:02**, and Carbamazepine

Chung et al., *Nature* 2004;428:486. *Cw*0801, *A*1101 and *DRB1*1202 within the HLA region occurred at increased frequency.

**HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans**

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D., John J. Farrell, M.S., Dalia Kasperavičiūtė, Ph.D., Mary Carrington, Ph.D., Graeme J. Sills, Ph.D., Tony Marson, M.B., Ch.B., M.D., Xiaoming Jia, M.Eng.
SJS/TEN, *HLA-B*15:02, and Carbamazepine


Cw*0801*, A*1101 and DRB1*1202 within the HLA region occurred at increased frequency.

SJS/TEN OR = 26

All Hypersensitivity OR = 9.1
## HLA Alleles Associated with SJS/TEN

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA Allele</th>
<th>Population</th>
<th>OR</th>
<th>NPV*</th>
<th>PPV*</th>
<th>NNT to prevent &quot;1&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>B*57:01</td>
<td>5%-8% White, &lt;1% African/Asian, 2.5% Black</td>
<td>960</td>
<td>100% for patch test confirmed</td>
<td>55%</td>
<td>13</td>
</tr>
<tr>
<td>Allopurinol SJS/TEN and DRESS/DIHs</td>
<td>B*58:01</td>
<td>9%-11% Han Chinese, 1%-6% White</td>
<td>&gt;800</td>
<td>100% in Han Chinese</td>
<td>3%</td>
<td>250</td>
</tr>
<tr>
<td>Carbamazepine SJS/TEN</td>
<td>B*15:02</td>
<td>10%-15% Han Chinese, &lt;0.1% White</td>
<td>&gt;1000</td>
<td>100% in Han Chinese (with other B75 serotype)</td>
<td>3%</td>
<td>1,000</td>
</tr>
<tr>
<td>Carbamazepine DRESS</td>
<td>A*31:01</td>
<td>Chinese, Europeans, Japanese</td>
<td>9.5</td>
<td>99.97%</td>
<td>0.59%</td>
<td>5,000</td>
</tr>
<tr>
<td>Dapsone DRESS/DIHs</td>
<td>B*13:01</td>
<td>2%-20% Chinese, 28% Papuans/Australian Aboriginals, 0% European/African, 1.5% Japanese</td>
<td>20</td>
<td>99.8%</td>
<td>7.8%</td>
<td>84</td>
</tr>
<tr>
<td>Flucloxacillin (drug-induced liver disease)</td>
<td>B*57:01</td>
<td>5%-8% White, &lt;1% African/Asian, 2.5% Black</td>
<td>81</td>
<td>99.99</td>
<td>0.14%</td>
<td>13,819</td>
</tr>
<tr>
<td>Nevirapine DRESS</td>
<td>C*04:01</td>
<td>&gt;10%</td>
<td>3-7</td>
<td>95.97</td>
<td>5%-27%</td>
<td>Variable</td>
</tr>
<tr>
<td>Methimazole/carbamazole Antithyroid drugs (agranulocytosis)</td>
<td>B<em>38:02, B</em>27:05</td>
<td>5%-15% China, Taiwan, 3%-4% European HLA-B*27:05</td>
<td>266</td>
<td>99.9</td>
<td>7%</td>
<td>211</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>753</td>
<td>&gt;99%</td>
<td>30%</td>
<td>238</td>
</tr>
</tbody>
</table>

*NPV: Negative predictive value, PPV: Positive predictive value, NNT: Number needed to test to prevent 1 case.

### High Incidence of SJS/TEN in Thailand

**Drug induced SJS/TENs in Thailand 1998-2008**

(Reference: Thai FDA 2008)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SULFAMETHOXAZOLE+ TRIMETHOPRIM</td>
<td>1,234</td>
</tr>
<tr>
<td>2. CARBAMAZEPINE</td>
<td>703</td>
</tr>
<tr>
<td>3. ALLOPURINOL</td>
<td>664</td>
</tr>
<tr>
<td>4. PHENYTOIN</td>
<td>451</td>
</tr>
<tr>
<td>5. AMOXICILLIN</td>
<td>342</td>
</tr>
<tr>
<td>6. STAVUDINE + LAMIVUDINE+NEVIRAPINE</td>
<td>313</td>
</tr>
<tr>
<td>7. PHENOBARBITAL</td>
<td>189</td>
</tr>
<tr>
<td>8. IBUPROFEN</td>
<td>156</td>
</tr>
<tr>
<td>9. NEVIRAPINE</td>
<td>122</td>
</tr>
<tr>
<td>10. TETRACYCLINE</td>
<td>113</td>
</tr>
</tbody>
</table>

**Genomic markers have been found and utilized as predictive tools by our group.**

Courtesy W Chantratita, Ramathibodi Hospital
<table>
<thead>
<tr>
<th>Name &amp; Family Name</th>
<th>Outcome of the PGX assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 Jan 2014</td>
</tr>
<tr>
<td>PGx Interpretation</td>
<td>High Risk of SJS/TEN from Carbamazepine, according to update information</td>
</tr>
</tbody>
</table>

**Suggestion:** According to update information, this person has HLA-B*1502 which has a high risk to develop a severe skin disorder (SJS/TEN), if he takes carbamazepine or drug structurally similar.

**Need more information:** please contact our PGx laboratory. Tel 02-200-4330-3...

Courtesy W Chantratita
SJS/TEN is Declining in Thailand (1998-2018)

US FDA alert

Brainstorming

Nation-wide testing

Number of Cases

0 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000 11000 12000 13000 14000 15000 16000


Courtesy S. Mahasirimongkol, Data source, Health Product Vigilance Center, Thai FDA, December, 2018
Development of powerful and barrier-free CDSS

http://safety-code.org/

Point of Care PGx Information

Scan QR code

U-PGx | Ubiquitous Pharmacogenomics

U-PGx | Ubiquitous Pharmacogenomics

Name: Jane Doe
Date of birth: 01.02.1934

Gene, status | Critical drug substances (modification recommended!)
--- | ---
CYP2C19 | Clopidogrel, Sertraline
Poor metabolizer
CYP2D6 | Amoxiptiline, Arpiprazole, Clomipramine, Codeine, Dextroprin, Haloperidol, Imipramine, Metoprolol, Nortriptyline, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine
Ultrarapid metabolizer
TPMT | Azathioprine, Mercaptopurine, Thioguanine
Poor metabolizer
Other genes
Not actionable
A3B1, ADRA1, BRCA1, COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP3A4, CYP3A5, DPD, G6PD, HMGCR, P2RY12, SULT1A1, UGT1A1, VKORC1

Date printed: 10.12.2015
Card number: 0000001

Dutch Pharmacogenetics Working Group guideline
Reason: TPMT: poor metabolizer
Select alternative drug or reduce dose by 90%. Increase dose in response of hematogetic monitoring and efficacy.
Date of evidence: March 16, 2015

- Azathioprine (1)
- Mercaptopurine (1)
- Thioguanine (1)
Pharmacogenetics

Pharmacogenetics (or pharmacogenomics) is the study of genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as side effects. In the Netherlands pharmacists can request the available pharmacogenetic data if the patient has given consent.
Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group

PCD Bank\textsuperscript{1}, KE Caudle\textsuperscript{2}, JJ Swen\textsuperscript{1}, RS Gammal\textsuperscript{2,3}, M Whirl-Carrillo\textsuperscript{4}, TE Klein\textsuperscript{4}, MV Relling\textsuperscript{2} and H-J Guchelaar\textsuperscript{1}

Both the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group provide therapeutic recommendations for well-known gene-drug pairs. Published recommendations show a high rate of concordance. However, as a result of different guideline development methods used by these two consortia, differences between the published guidelines exist. The aim of this paper is to compare both initiatives and explore these differences, with the objective to achieve harmonization.
Geographic Differences in Drug Hypersensitivity

Genes Mirror Geography in Europe

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  • Capturing evidence

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**Genetic Diagnosis in Undiagnosed Disease Network (UDN)**

- 382 evaluated patients
- 132 received diagnosis (35%)
  - 98 diagnoses made by sequencing (74%)
  - 21% led to recommended changes in therapy
  - 37% led to changes in diagnostic testing
  - 36% led to variant-specific genetic counseling
Yield and Speed of Genome Sequencing Diagnosis in Critically Ill Infants

- 65 infants < 4mo age in NICU/PICU, trios
- 31% diagnoses in “WGS + standard,” 3% “standard”
- Time to dx: 13 days [1-84] vs. 107 days [21-429]
Yield and Speed of Genome Sequencing Diagnosis in Critically Ill Infants

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  - Capturing evidence
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- **Resources**
- **Collaborations**
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More Detailed Information on Key Tier 1 Applications – Hereditary Breast and Ovarian Cancer (HBOC)

What is hereditary breast and ovarian cancer and how does it affect risk of cancer?
More Detailed Information on Key Genomic Applications Tier 1

Hereditary Breast and Ovarian Cancer (HBOC) Tools

Tools for Bidirectional Cancer Registry Reporting to Identify Individuals at Risk for Hereditary Breast and Ovarian Cancer syndrome

The following materials were developed to support state programs using bidirectional cancer registry reporting to identify individuals at risk for Hereditary Breast and Ovarian Cancer syndrome. State health departments are encouraged to customize the materials to meet their needs. Materials are categorized by those intended for patients and for healthcare providers, but materials may be suitable for multiple audiences. Please note that some materials will need to be filled out with state-specific information, as noted below.

Risk of cancer?
More Detailed Information on Key Tier 1 Applications – Familial Hypercholesterolemia

https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
U.S. Centers for Disease Control and Prevention Tier 1 Genomic Applications

https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
U.S. Centers for Disease Control and Prevention Tier 1 Genomic Applications

Familial Hypercholesterolemia Mutation

- No
- Yes

Odds Ratio for Coronary Artery Disease (95% CI)

- LDL Cholesterol Category (mg/dl)
  - <130
  - ≥130-160
  - ≥160-190
  - ≥190-220
  - ≥220

- LDL Cholesterol (mg/dl)

https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
Overlap of LDL-C Levels in 26,025 Persons with and without FH Mutations

Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Douglas F. Easton, Ph.D., and Bruce A.J. Ponder, F.R.S.

Polygenic risk and the development and course of asthma: an analysis of data from a four-decade longitudinal study

Daniel W Belsky, Malcolm R Sears, Robert J Hancox, Honalee Harrington, Renate Houts, Terrie E Moffitt, Karen Sugden, Benjamin Williams, Richie Poulton, Avshalom Caspi

Summary

Background Genome-wide association studies (GWAS) have discovered genetic variants that predispose individuals to asthma. To integrate these new discoveries with emerging models of asthma pathobiology, we aimed to test how genetic discoveries relate to developmental and biological characteristics of asthma.

Polygenic Risk Scores (PRS)

• Breast Cancer
• Prostate Cancer
• Coronary Disease
• Alzheimer Disease
• Bone Density

Genetic assessment of age-associated Alzheimer disease risk: Development and validation

Implications of polygenic risk-stratified screening for prostate cancer on overdiagnosis

• Asthma
• Autism
• ADHD
• T1 Diabetes
• T2 Diabetes
Polygenic Risk Scores (PRS)

<table>
<thead>
<tr>
<th>GPS Cut-Off</th>
<th>Reference Group</th>
<th>Odds Ratio</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Coronary Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top 20%</td>
<td>Remaining 80%</td>
<td><strong>2.55</strong></td>
<td>[2.43, 2.67]</td>
<td>&lt; 1 x 10^{-300}</td>
</tr>
<tr>
<td>Top 10%</td>
<td>Remaining 90%</td>
<td><strong>2.89</strong></td>
<td>[2.74, 3.05]</td>
<td>&lt; 1 x 10^{-300}</td>
</tr>
<tr>
<td>Top 5%</td>
<td>Remaining 95%</td>
<td><strong>3.34</strong></td>
<td>[3.12, 3.58]</td>
<td>6.5 x 10^{-264}</td>
</tr>
<tr>
<td>Top 1%</td>
<td>Remaining 99%</td>
<td><strong>4.83</strong></td>
<td>[4.25, 5.46]</td>
<td>1.0 x 10^{-132}</td>
</tr>
<tr>
<td>Top 0.5%</td>
<td>Remaining 99.5%</td>
<td><strong>5.17</strong></td>
<td>[4.34, 6.12]</td>
<td>7.9 x 10^{-78}</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Inflammatory Bowel Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top 20%</td>
<td>Remaining 80%</td>
<td><strong>2.19</strong></td>
<td>[2.03, 2.36]</td>
<td>7.7 x 10^{-95}</td>
</tr>
<tr>
<td>Top 10%</td>
<td>Remaining 90%</td>
<td><strong>2.43</strong></td>
<td>[2.22, 2.65]</td>
<td>8.8 x 10^{-88}</td>
</tr>
<tr>
<td>Top 5%</td>
<td>Remaining 95%</td>
<td><strong>2.66</strong></td>
<td>[2.38, 2.96]</td>
<td>3.0 x 10^{-68}</td>
</tr>
<tr>
<td>Top 1%</td>
<td>Remaining 99%</td>
<td><strong>3.87</strong></td>
<td>[3.18, 4.66]</td>
<td>1.4 x 10^{-43}</td>
</tr>
<tr>
<td>Top 0.5%</td>
<td>Remaining 99.5%</td>
<td><strong>4.81</strong></td>
<td>[3.74, 6.08]</td>
<td>9.0 x 10^{-37}</td>
</tr>
</tbody>
</table>

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• Opportunities
  – Pharmacogenomics
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Beyond Developing the Perfect Genetic/Genomic Test

Even if a genetic test can identify optimal treatment for a specific illness or reduce risk for health problems, if:

- Only half of insurers/ministries choose to provide it;
- Half of health systems train clinicians to prescribe it;
- Half of clinicians at those systems prescribe it; and
- Half of their patients get tested

And assuming perfect access/testing/follow-up:

**Impact:** 50% x 50% x 50% x 50% = 6% benefit

Adapted from D. Chambers and R. Glasgow, NCI
Definitions and Goals of Dissemination and Implementation Research

• *Dissemination research*:  
  • Study of targeted distribution of information and intervention materials to specific public health or clinical practice audience  
  • Goal: to understand how best to spread and sustain knowledge and associated evidence-based interventions

• *Implementation research*:  
  • Study of strategies to adopt evidence-based health interventions into clinical and community settings  
  • Goal: to improve patient outcomes and benefit population health

Adapted from D. Chambers, NCI
Implementation Research in Genomic Medicine

- Studies of the local adaptation of evidence-based practices in the context of implementation
- Longitudinal and follow-up studies on the factors that contribute to the sustainability of evidence-based interventions
- Scaling up health care interventions across health plans, system and networks
- De-implementation of ineffective or suboptimal care
De-Implementation: SCN5A and Sudden Arrhythmic Death

De-Implementation: SCN5A and Sudden Arrhythmic Death

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OUR FOCUS

We want to make effective treatment optimization accessible to every European citizen
Clinical Genome Resource (ClinGen)
ClinGen Goals

• Create standard curation approach and authoritative resource to define clinical relevance of genes and variants for use in research and care

• Establish semi-quantitative framework to assess strength of evidence for role of specific genes in specific diseases

• Promote public sharing of variant interpretations, use of common standards, terminology

• Improve, disseminate rules for variant interpretation

• Resolve inter-laboratory conflicts

• Engage experts in systematic consensus driven interpretation of variants (Expert Panels)
ClinGen Working Group and Expert Panel Membership

850 researchers & clinicians from 27 countries

[Created by Natalie Pino, Oct. 2018]
488,088 unique variants submitted to ClinVar from 1,122 submitters across 67 countries

Division of Genomic Medicine

Genomic Medicine Activities

As detailed in its 2011 Strategic Plan, NHGRI has been pursuing a number of activities in genomic medicine implementation. Links to NHGRI’s current initiatives are listed below:

Notable Accomplishments in Genomic Medicine

A list of significant advances in the realm of genomic medicine for 2011-2012, compiled by the NHGRI Genomic Medicine Working Group. The list is updated every month.

- Go to: Notable Accomplishments in Genomic Medicine

Genomic Medicine Meetings

NHGRI held a series of Genomic Medicine meetings gathering genomics researchers, clinicians, and other experts from over U.S. institutions involved with the implementation of genomic medicine programs. The goal of these meetings includes identifying research gaps and opportunities, sharing approaches to genomic medicine implementation, and facilitating development of an active research
43,354 unique variants submitted to ClinVar from 391 submitters across 27 European countries

Notable Accomplishments in Genomic Medicine

The NHGRI Genomic Medicine Working Group has compiled a list of interesting advances in the field.

Clinical Implementation

2018

- July: Opportunities to implement a sustainable genomic medicine program: lessons learned from care delivery and reimbursement [ncbi.nlm.nih.gov]
- April: Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization [ncbi.nlm.nih.gov]
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If you find a path with no obstacles, it probably doesn’t lead anywhere.

Frank A. Clark
Integrating Genomics into Personalised Healthcare

- Opportunities
- Obstacles
- Resources
  - NHGRI Genomic Medicine Activities
  - Genomic Medicine Meetings
  - Inter-Society Coordinating Committee for Practitioner Education in Genomics
  - Global Genomic Medicine Collaborative (G2MC)
  - Implementing Genomics in Practice (IGNITE)
- Collaborations
Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera, Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, Eric S. Lander, Steven A. Lubitz, Patrick T. Ellinor and Sekar Kathiresan
Notable Accomplishments in Genomic Medicine

Genome-wide polygenic scores for common disease identify individuals with risk equivalent to monogenic mutations

Amit V. Khera1,2,3,4, Mark Chaffin4, Krishna G. Aragam1,2,3,4, Mary C. Haed4, Carolina Roselli4,4, Seung Hoan Choi4, Pradeep Natarajan4, Eric S. Linder4,5, Lubitz4,5, Patrick T. Ellinor1,2,3,4, and Sekar Kathiresan4,5,*
Implementing genomic medicine in the clinic: the future is here

Teri A. Manolio, MD, PhD1, Rex L. Chisholm, PhD2, Brad Ozenberger, PhD1, Dan M. Roden, MD3, Marc S. Williams, MD4,5, Richard Wilson, PhD6, David Bick, MD7, Erwin P. Bottinger, MD8, Murray H. Brilliant, PhD9, Charis Eng, MD, PhD10, Kelly A. Frazer, PhD11, Bruce Korf, MD, PhD12, David H. Ledbetter, PhD5, James R. Lupski, MD, PhD13, Clay Marsh, MD14, David Mrazek, MD15, Michael F. Murray, MD16, Peter H. O’Donnell, MD17, Daniel J. Rader, MD18, Mary V. Relling, PharmD19, Alan R. Shuldiner, MD20, David Valle, MD21, Richard Weinshilboum, MD22, Eric D. Green, MD, PhD1 and Geoffrey S. Ginsburg, MD, PhD23

Although the potential for genomics to contribute to clinical care has long been anticipated, the pace of defining the risks and benefits of incorporating genomic findings into medical practice has been relevant: lack of reimbursement for genomically driven interventions and burden to patients and clinicians of assaying, reporting, intervening, and following up genomic findings. Key infrastructure needs
Integrating Genomics into Personalised Healthcare

• Opportunities
• Obstacles

• Resources
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  – Implementing Genomics in Practice (IGNITE)

• Collaborations
On September 5-6, 2018, the National Human Genome Research Institute (NHGRI) sponsored its 11th Genomic Medicine meeting - Genomic Medicine XI: Research Directions in Genomic Medicine Implementation - at the Hilton La Jolla Torrey Pines hotel in La Jolla, California.
### Wednesday, September 5

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 a.m.</td>
<td>Welcome and Introductions</td>
<td>Rex Chisholm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teri Manolio</td>
</tr>
<tr>
<td>8:45 a.m.</td>
<td>Overview of NHGRI's 'Genomics 2020' strategic planning process</td>
<td>Eric Green</td>
</tr>
<tr>
<td></td>
<td>Slides</td>
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</tr>
</tbody>
</table>

Session 1: Basics of implementation science and its relation to genomic medicine

Moderator: Geoff Ginsburg
CYP2C19 - Clopidogrel
## Genomic Medicine Meetings

### Wednesday, September 20

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Slides</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 a.m.</td>
<td>Welcome and Overview</td>
<td></td>
</tr>
<tr>
<td>8:45 a.m.</td>
<td>CYP2C19 - Clopidogrel</td>
<td></td>
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</tbody>
</table>

**CYP2C19 - Clopidogrel**

- Evidence Overview: CYP2C19 – Clopidogrel
- Clinical Pharmacogenetics Implementation Consortium Guideline Resources: CYP2C19 – Clopidogrel
- PharmGKB Resources: CYP2C19 – Clopidogrel
- Genotyping Resources: CYP2C19 – Clopidogrel
- Implementation Workflow Examples: CYP2C19 – Clopidogrel
- Clinical Decision Support: CYP2C19 – Clopidogrel
- Data Collection and Implementation Metrics: CYP2C19 – Clopidogrel
- Resources for Patients and Providers: CYP2C19 – Clopidogrel

Genomic Medicine Meetings

On September 20, 2017, the National Human Genome Research Institute (NHGRI) hosted a meeting on "Genomic Medicine for Precision Medicine" at the NHGRI in Bethesda, MD. The meeting was focused on discussing the latest advancements in genomic medicine and their applications in precision medicine.

- **Time:** 8:30 a.m. – 4:30 p.m.
- **Location:** NHGRI, Bethesda, MD
- **Topics:**
  - Welcome and Overview
  - CYP2C19 – Clopidogrel
  - Evidence Overview
  - Clinical Pharmacogenetics Implementation Consortium Guideline Resources
  - PharmGKB Resources
  - Genotyping Resources
  - Implementation Workflow Examples
  - Clinical Decision Support
  - Data Collection and Implementation Metrics
  - Resources for Patients and Providers

The meeting aimed to provide a platform for experts in the field to share their insights and experiences, fostering collaboration and innovation in genomic medicine.
Integrating Genomics into Personalised Healthcare

• Opportunities
• Obstacles
• Resources
  – NHGRI Genomic Medicine Activities
  – Genomic Medicine Meetings
  – Inter-Society Coordinating Committee for Practitioner Education in Genomics
  – Global Genomic Medicine Collaborative (G2MC)
  – Implementing Genomics in Practice (IGNITE)
• Collaborations
Integrating Genomics into Personalised Healthcare

• Opportunities
• Obstacles

• Resources
  – NHGRI Genomic Medicine Activities
  – Genomic Medicine Meetings
  – Inter-Society Coordinating Committee for Practitioner Education in Genomics
  – Global Genomic Medicine Collaborative (G2MC)
  – Implementing Genomics in Practice (IGNITE)

• Collaborations
SITE: University of Florida  GENE/DRUG: CYP2C19/clopidogrel  TYPE: Clinical

Patient
- Patient undergoes PCI
- Prescriber orders CYP2C19 test
- Phlebotomist/nurse obtains sample and sends to lab
- Prescriber orders clopidogrel
- Patient and prescriber discuss treatment decision

Clinical Team
- Clinical Information Systems
  - In-basket EMR message sent to clinical pharmacy
- Labs
  - Clinical lab performs CYP2C19 genotype test
  - Clinical lab adds result to Epic
- Pharmacist
  - Pharmacist reviews patient chart for needed follow up
  - Pharmacist reviews alternative therapies with interventionalist team

Genetic Counselor

Research Coordinator

Developed by the UF Health Personalized Medicine Program (2012). For questions regarding this resource, visit our website (personalizedmedicine.ufhealth.org) or contact: PMP-HELP@ctsi.ufl.edu.
Integrating Genomics into Personalised Healthcare

- Opportunities
- Obstacles
- Resources
- Collaborations
  - Implement PGx testing for frequent risk alleles
  - Find ways to randomize implementation, even if only in time received (“stepped wedge RCT”)
  - Implement genome-first approach to undiagnosed diseases and critically ill infants
  - Exploit natural genomic variation of Europe in assessing genetic influences on drug response
Integrating Genomics into Personalised Healthcare – Collaborations (continued)

- Collaborations
  - Move forward with best available evidence meeting agreed-upon standards
  - Apply implementation research methods to determine *how* best to implement locally
  - Engage professional societies in guideline development and dissemination
  - Deposit data as widely as possible: EGA, ClinVar
  - Participate in scientific community approaches such as ClinGen, GA4GH activities
Genomics is Global
Integrating Genomics into Personalised Healthcare: We Need Not Be Alone
Creating a Universe of Possibilities

“As for the future, your task is not to foresee it, but to enable it.”

~ Antoine de Saint Exupéry
Many Thanks…

Joy Boyer
Lisa Brooks
Heather Colley
Erin Currey
Alvaro Encinas
Eric Green
Sarah Gould
Sarita Gupta
Lucia Hindorff
Jean Jenkins
Sheethal Jose
Dave Kaufman
Rongling Li
Nicole Lockhart
Ebony Madden

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Donna Messersmith
Kiara Palmer
Erin Ramos
Robb Rowley
Laura Rodriguez
Cecelia Tamburro
Simona Volpi
Ken Wiley
Anastasia Wise
Carol Bult, Rex Chisholm,
Pat Deverka, Geoff Ginsburg,
Howard McLeod, George
Mensah, Mary Relling, Dan
Roden, Marc Williams

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Mensah, Mary Relling, Dan
Roden, Marc Williams
## NHGRI’s Genomic Medicine Research Program

<table>
<thead>
<tr>
<th>Program</th>
<th>Goal</th>
<th>Σ$M</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UDN</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Diagnose rare and new diseases by expanding NIH’s Undiagnosed Diseases Program</td>
<td>237</td>
<td>FY13-22</td>
</tr>
<tr>
<td><strong>NSIGHT</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Explore possible uses of genomic sequence information in the newborn period</td>
<td>26</td>
<td>FY13-18</td>
</tr>
<tr>
<td><strong>CSER</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Generate evidence of clinical utility of sequencing in diverse clinical settings</td>
<td>166</td>
<td>FY12-20</td>
</tr>
<tr>
<td><strong>eMERGE</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Use biorepositories with EMRs for genomics; assess penetrance of clinically relevant genes</td>
<td>141</td>
<td>FY07-19</td>
</tr>
<tr>
<td><strong>IGNITE</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Develop and disseminate methods for incorporating patients’ genomic findings into their clinical care</td>
<td>76</td>
<td>FY13-22</td>
</tr>
<tr>
<td><strong>ClinGen</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Develop and disseminate consensus information on genes and variants relevant to clinical care</td>
<td>73</td>
<td>FY13-20</td>
</tr>
<tr>
<td><strong>Investigator-Initiated</strong></td>
<td>Clinical sequencing research, HIV/AIDS drug response and co-morbidities, serious ADRs, pharmacogenomics</td>
<td>42</td>
<td>FY15-22</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td>Institutional training grants, fellowships, career development</td>
<td>16</td>
<td>FY16-21</td>
</tr>
</tbody>
</table>

<sup>1</sup> NIH Common Fund; <sup>2</sup> Co-Funded by NICHD; <sup>3</sup> Co-Funded by NCI; <sup>4</sup> Co-Funded by OD.
Spectrum of Genomic Medicine Implementation: Intensity vs. Breadth

- **Depth of Patient Characterization**
- **Breadth of Implementation**

- ClinGen
  - System-Wide Impact
  - Evidence Generation
  - Testing Multiple Models
  - Impact on Clinicians, Labs

- UDN
- CSER
- NSIGHT
- IGNITE
- eMERGE
- NSIGHT

- **Individual Patient Focus**
- **Testing Multiple Models**
- **System-Wide Impact**
203 middle-aged adults at intermediate risk

Randomized to receive 10-yr CHD risk estimates from clinical risk alone (CRS) or clinical risk + genetic risk (+GRS)

Compared LDL-C at 6 mos

Any differences due to diet, activity, statins

Kullo I et al., Circulation. 2016;133:1181-88.
LDL-C Lowering in Patients Given Clinical and Genomic Risk Information

“…Disclosure of CHD risk estimates that incorporated genetic risk information led to lower LDL-C levels than disclosure of CHD risk based on conventional risk factors alone.”

Kullo I et al., Circulation. 2016;133:1181-88.
Tier 1 Genomics Applications and their Importance to Public Health

Tier 1 genomic applications are defined by CDC's Office of Public Health Genomics (OPHG) as those having significant potential for positive impact on public health based on available evidence-based guidelines and recommendations. Tier 1 applications are listed in the Genomic Tests and Family History by Levels of Evidence Table which includes a growing number of genomics tests and family health history applications.

Presently, this toolkit focuses on three Tier 1 applications. Nearly 2 million people in the United States are at increased risk for adverse health outcomes because they have genetic mutations which predispose them to one of the following conditions:
• Hereditary Breast and Ovarian Cancer Syndrome (HBOC) - increased risk for breast, ovarian, tubal, peritoneal, and other cancers due to mutations in BRCA1 or BRCA2 genes;

• Lynch syndrome (LS) - increased risk for colorectal, endometrial, ovarian, and other cancers associated with mutations in mismatch-repair genes; or

• Familial hypercholesterolemia (FH) - increased risk for heart disease or stroke due to mutations leading to very high cholesterol levels from an early age
**Secondary Findings from Exomes and Genomes**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer syndromes</td>
<td><strong>BRCA1, BRCA2, TP53, STK11, MLH1, MLH2, MSH6, PMS2, APC, MUTYH, BMPR1A, SMAD4, VHL, MEN1, RET, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1, NF2</strong></td>
</tr>
<tr>
<td>Cardiovascular syndromes</td>
<td><strong>COL3A1, FBN, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11, MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA, RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, KCNH2, SCN5A, LDLR, APOB, PCSK9</strong></td>
</tr>
<tr>
<td>Metabolic syndromes</td>
<td><strong>ATP7B, OTC, RYR1, CACNA1S</strong></td>
</tr>
</tbody>
</table>
Variant Classification Changes - HCM