



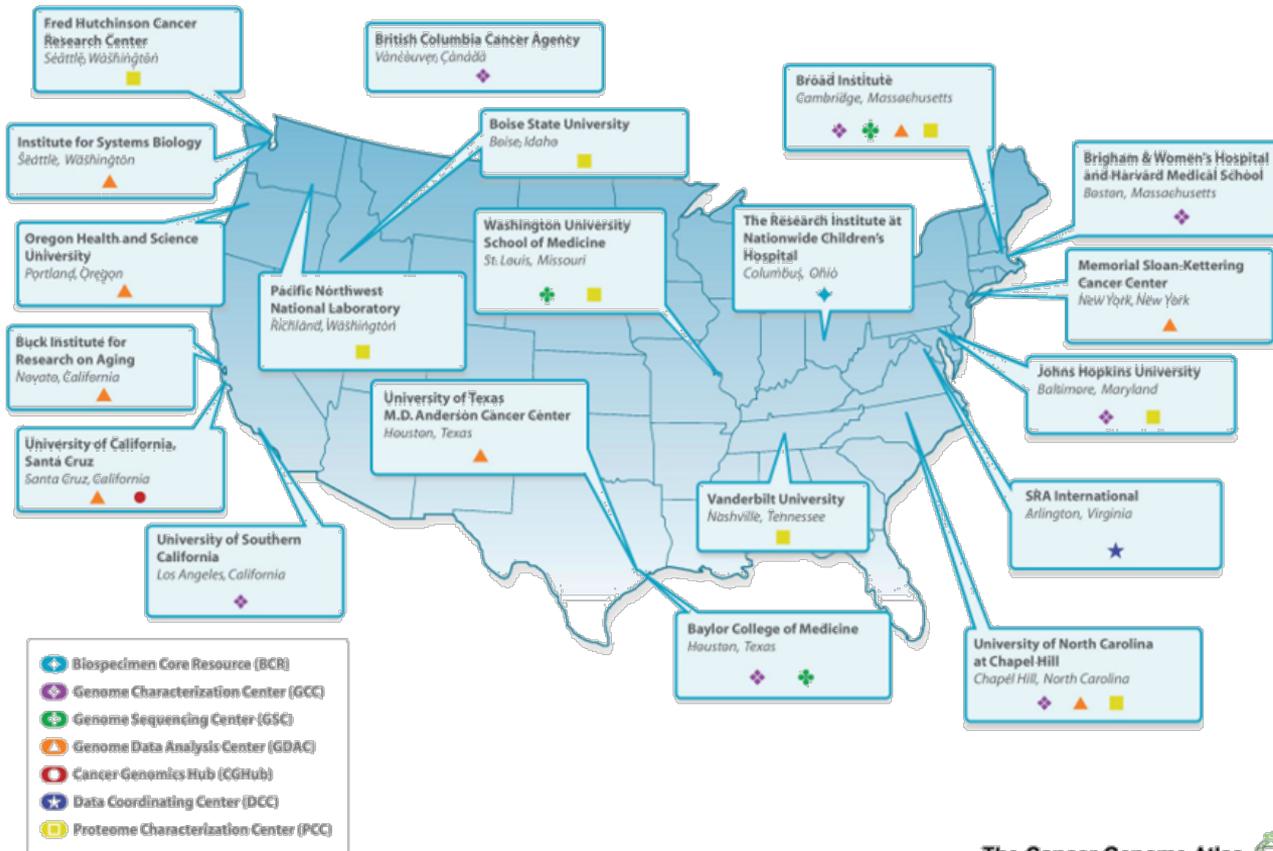
**Genomics: Insight and
Recommendations**
**Health Information Technology
Standards
Advisory Committee (HITSAC)**

Aaron Black
Director of Informatics
Inova Translational Medicine Institute
May 12th, 2016

- Introduction
 - Personal background
 - Inova Translational Medicine Institute(ITMI)
- Challenges
- Opportunities
- Process Recommendations
- Questions and Comments

– Personal Background

- Consulting
- Start-Up Company
 - Medical Billing
- The Cancer Genome Atlas (TCGA)
- Inova Translational Medicine Institute



Improve health of the diverse communities we serve through **application of genomics** and associated **molecular science** to drive “computation assisted”, intelligent **individualized care**

- Applied genomics
- Predictive wellness
- Disease risk management
- Pharmacogenomics

STARTED IN 2011

Research on the integration of genomic information into the practice of medicine

- >90 FTEs
- ~1/3 Clinical
- 1/3 IT/Informatics
- 1/3 Lab technical

ITMI Supports Over 12 Studies

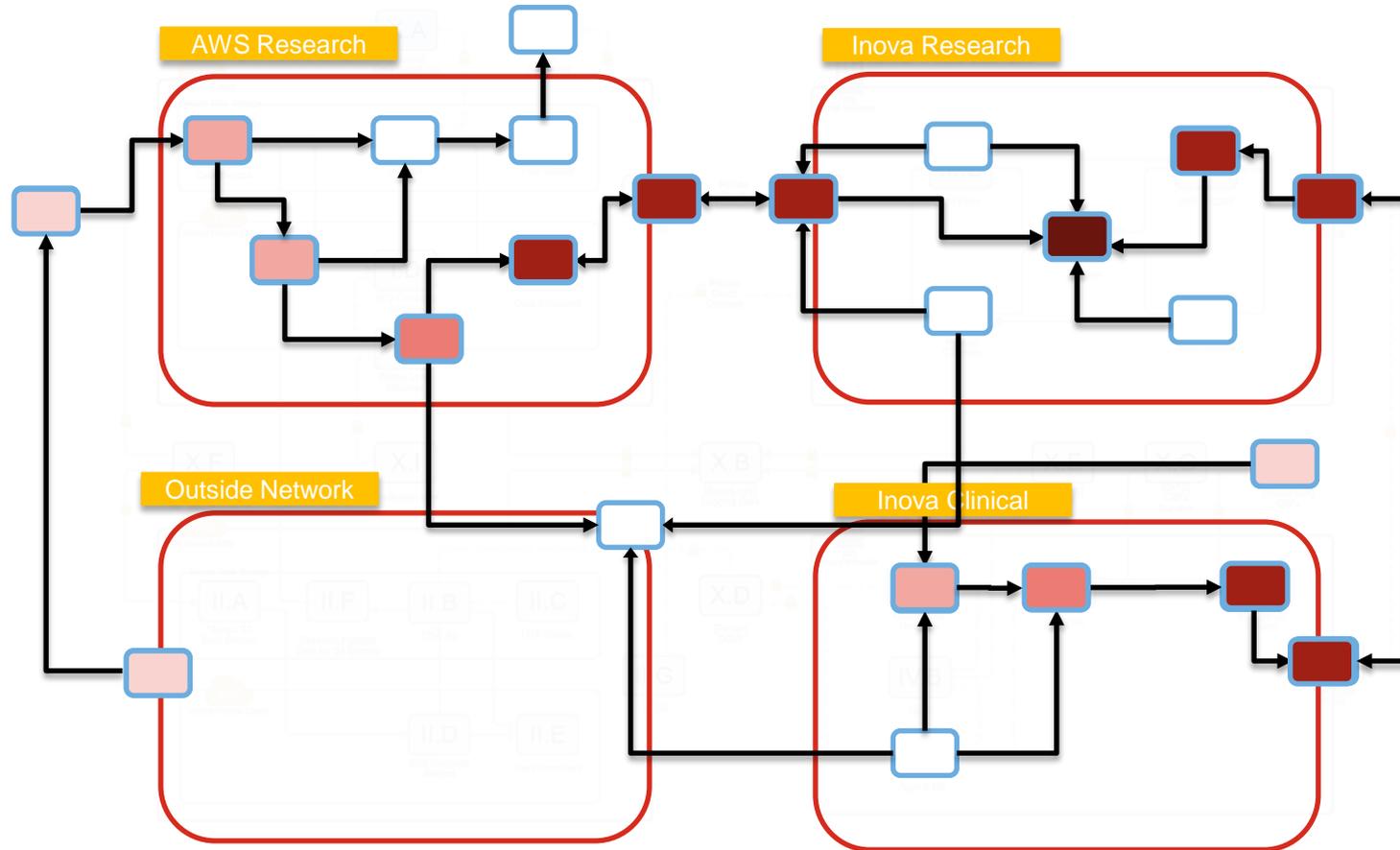
Pre-term birth study

★ Childhood Longitudinal
Cohort Study

Diseases of
the newborn

ITMI TODAY

- **3,476 families are enrolled in our studies**
- Preterm Birth has ~500 families, born <37 wks. (71 <28 wks.)
- ITMI has **9,000 whole genome sequences integrated with clinical electronic health record data** and study specific information in its data-set
- Maternal samples analyzed for RNAseq, methylation, expression
- There are **62,700 specimens including 1,427 placenta** samples in the ITMI biobank



IGL TODAY

- **Pharmacogenomics**

- Individual Drug specific tests

- Example - CLOPIDOGREL

- Panels

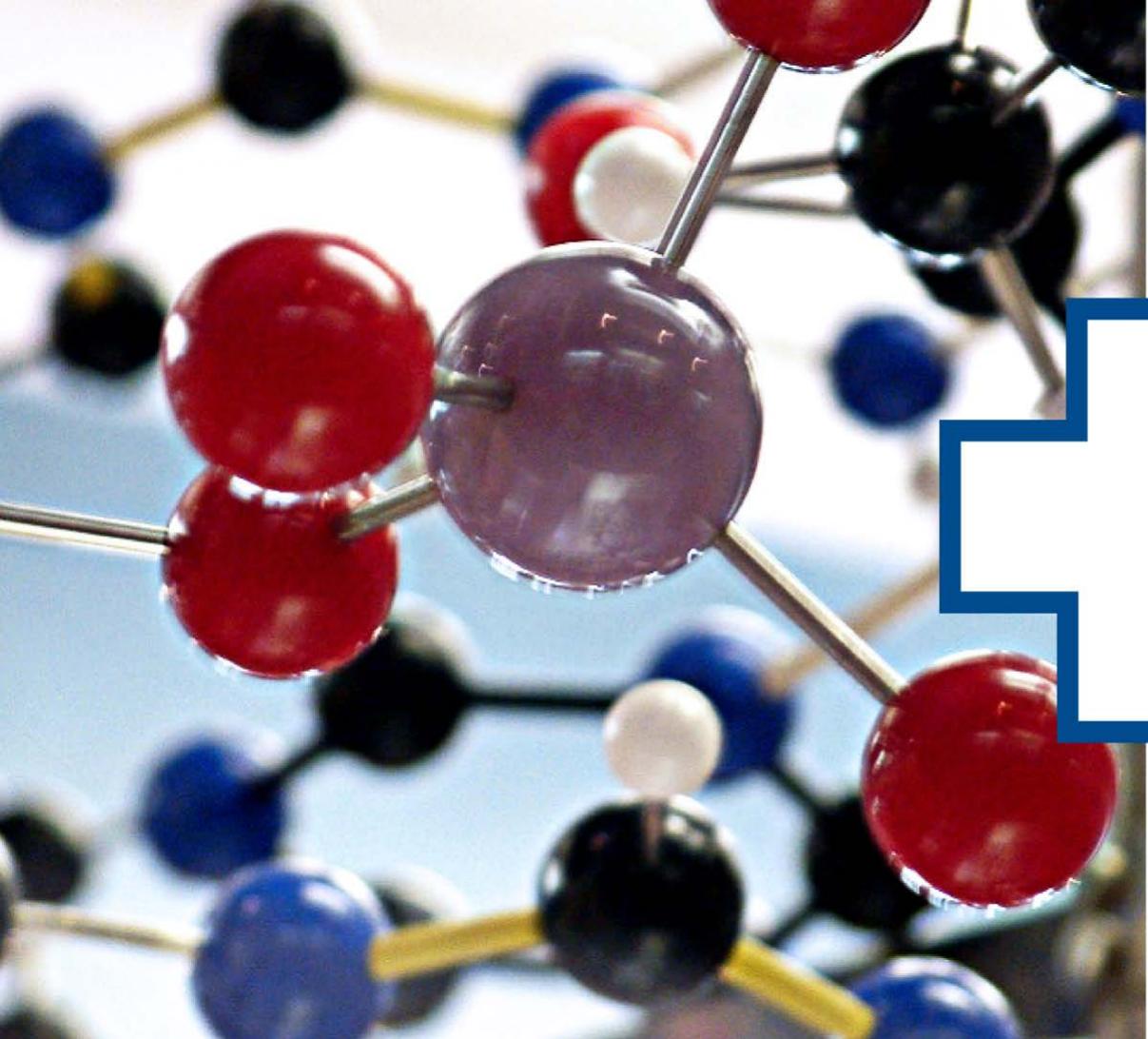
- MediMap

- **Cancer Panels**

- **Used for Inova Molecular Tumor Board**

Informatics

- **Pharmacogenomics**
 - Epic Integration
 - Custom Reports
 - Discrete results \ HL7 messaging
 - In process
 - Knowledgebase Vendor
 - *Translational Software*
- **Cancer Panels**
 - Cancer Hotspot \ Oncomine



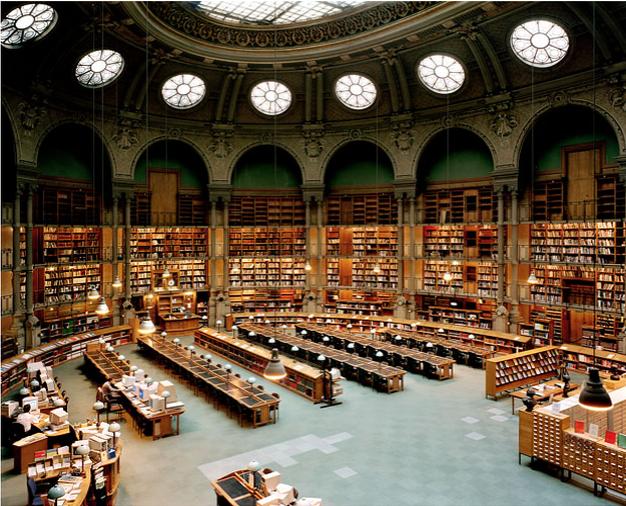
Challenges

- Inova - MediMap - <https://www.inova.org/itmi/medimap>
 - Pharmacogenomics (PGx) Panel
 - Infants at birth – Inova Fairfax Hospital
 - Consent needed from Mother
 - 7 Genes and their alleles (FDA Approved)
 - Large amount of tests (compared to other PGx Tests at Inova)

- Return of Results
 - Complicated
 - Needed concise summary – first page of report
 - Detailed followed later
- Pharmacogenomics is specialized
 - Knowledgebase
 - Annotations
- EHR not ready for Genetic \ Genomic results
- Customization needed for:
 - EHR, LIS, data processing, data exchange and reporting (just about everything)
- Standardization of genetic testing, Allele and Mutation coding is still developing
- Others are still using reports with little discrete return of results within EHR
- Data sizes small compared to other Next Generations Sequencing (NGS) tests

Data and Information

What we want it to look like!



Does it look more like?



- **Standardization**

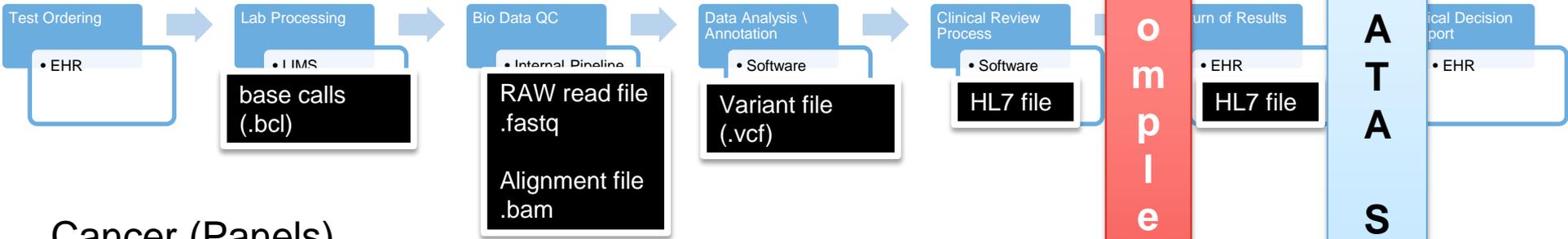
- **Healthcare System**

- Built for billing and government regulations
- Can be misleading for research
- EHRs, still new \ lack maturity for genetics \ genomic results

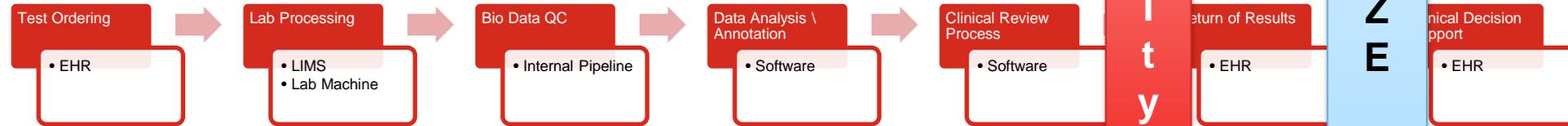
- **Research**

- Love the concept
- Hard to implement
- Always something new!

Pharmacogenomics (Panels)



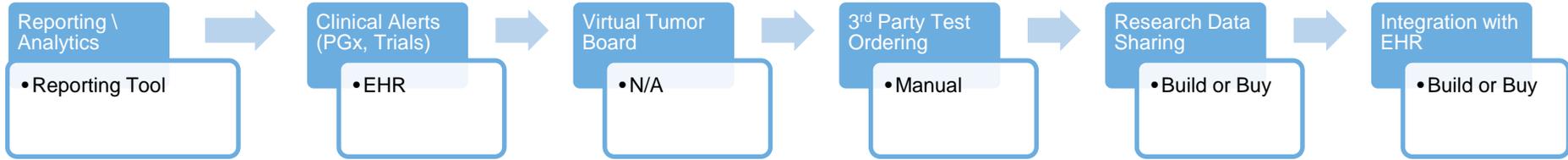
Cancer (Panels)



Whole Genome Sequencing ...etc

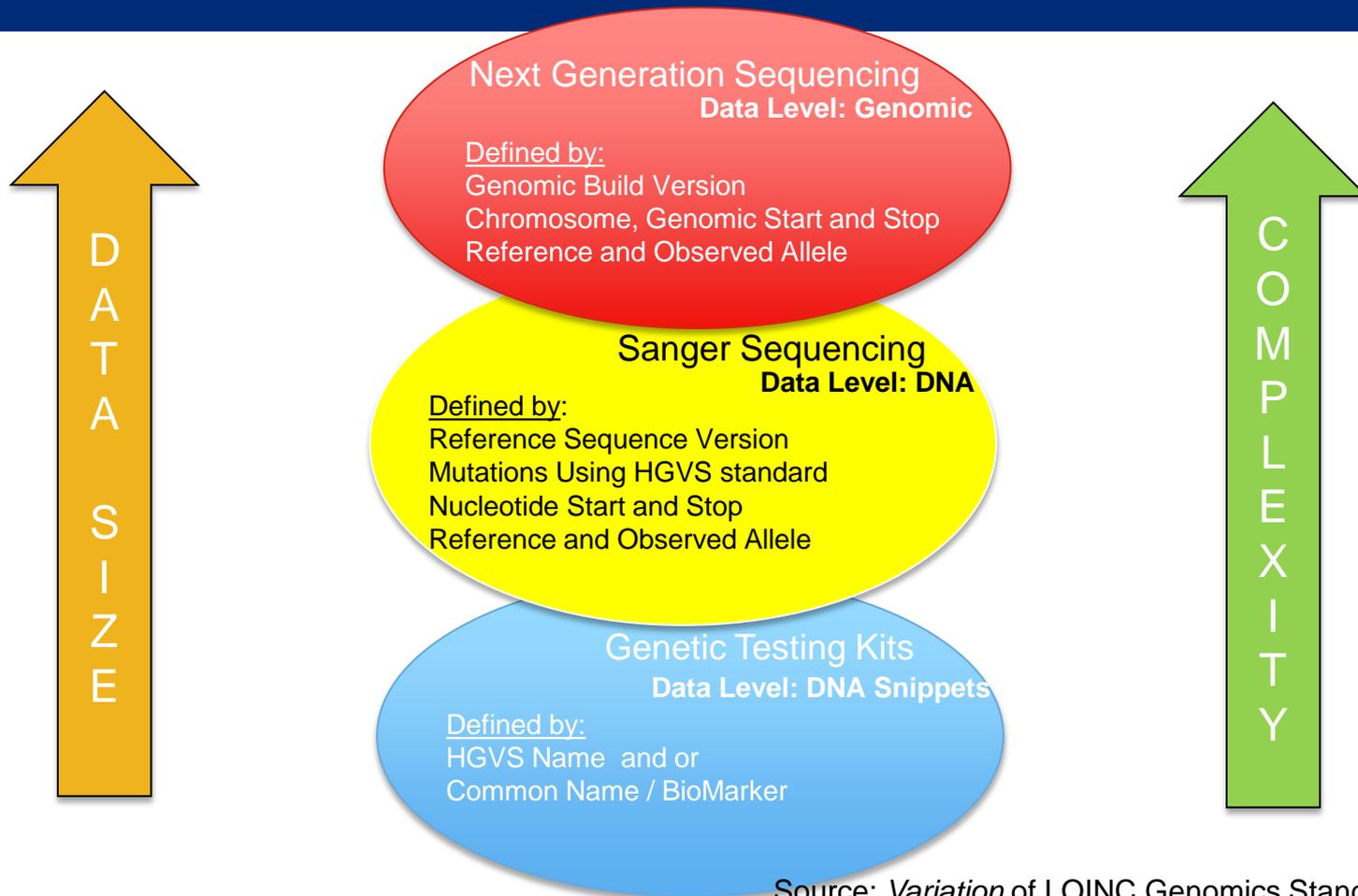


Pharmacogenomics (Panels)



Cancer (Panels)





- New tests and constantly changing knowledge
 - Many vendors don't have LOINC codes for their genetic tests
 - Codes inconsistently defined

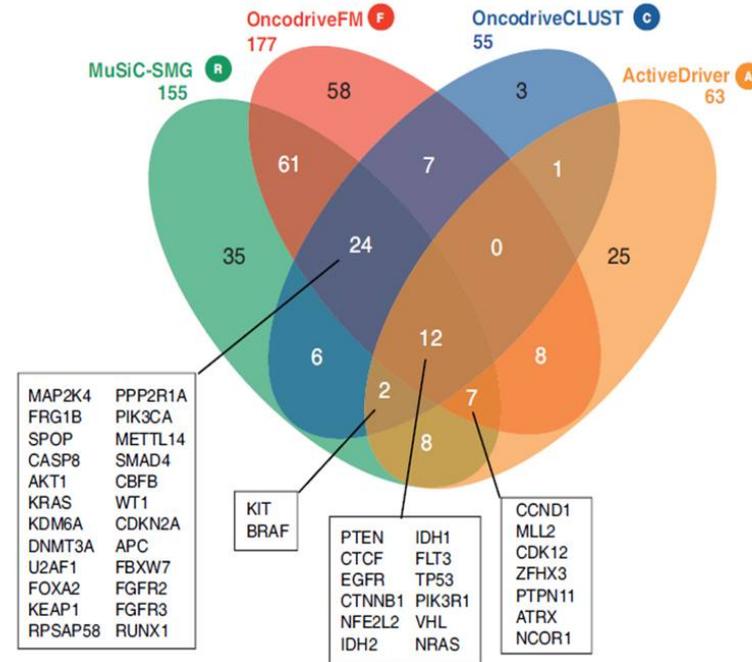
163	62360-3	Cells analyzed	Num	Pt	Bld/Tiss	Qn	Molgen	HL7.CYTOGEN	YH
164	62361-1	Cells counted	Num	Pt	Bld/Tiss	Qn	Molgen	HL7.CYTOGEN	YH
165	51779-7	CFH gene mutation analysis	Prid	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MUT	PH
166	42938-1	CFTR gene allele 1	Arb	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	AR
167	42939-9	CFTR gene allele 2	Arb	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	AR
168	46989-0	CFTR gene mutation analysis	Prid	Pt	Amnio fld	Nar	Molgen	MOLPATH.MUT	WK
169	38404-0	CFTR gene mutation analysis	Prid	Pt	Bld/Tiss	Nar	Molgen	MOLPATH.MUT	PH
170	21177-1	CFTR gene mutation analysis	Prid	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MUT	QS
171	34718-7	CFTR gene mutation analysis	Prid	Pt	Amnio fld	Nom	Molgen	MOLPATH.MUT	3M
172	21654-9	CFTR gene mutation analysis	Prid	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MUT	cjr
173	21656-4	CFTR gene mutations tested for	Prid	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MUT	cjr
174	50998-4	CFTR gene mutations tested for	Num	Pt	Bld/Tiss	Qn	Molgen	MOLPATH.MUT	GL
175	38449-5	CFTR gene.c.1078delT	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
176	38450-3	CFTR gene.c.2184delA	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
177	38451-1	CFTR gene.c.2789+5G>A	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
178	38452-9	CFTR gene.c.3120+1G>A	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
179	34706-2	CFTR gene.c.3199del6	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
180	38453-7	CFTR gene.c.3659delC	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
181	38456-0	CFTR gene.c.3849+10kbC>T	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
182	38455-2	CFTR gene.c.621+1G>T	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
183	38447-9	CFTR gene.c.711+1G>T	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
184	38448-7	CFTR gene.p.A455E	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
185	57930-0	CFTR gene.p.D1152H	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
186	21655-6	CFTR gene.p.F508del	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	cjr
187	38454-5	CFTR gene.p.G85E	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
188	43370-6	CFTR gene.p.IVS8 polyT	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	PH
189	53789-4	CFTR gene.p.IVS8 polyT 7T/9T variant	Arb	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	PH
190	34729-4	CFTR gene.p.R117H+5T variant	Pr	Pt	Bld/Tiss	Ord	Molgen	MOLPATH.MUT	3V
191	57931-8	CFTR+PRSS1+SPINK1 gene mutation analysis	Prid	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MUT	3V
192	42240-2	CHD7 gene mutation analysis	Prid	Pt	Bld/Tiss	Nar	Molgen	MOLPATH.MUT	PH
193	41749-3	CHIC2 gene mutation analysis	Prid	Pt	Bld/Tiss	Nar	Molgen	MOLPATH.MUT	PH
194	48000-4	Chromosome	ID	Pt	Bld/Tiss	Nom	Molgen	MOLPATH.MISC	CJ

- Definition of variants still being defined
- Single gene vs multi-gene
- Amplified with complex variants \ structural variants
- Difficult to nail down overall data standardization on genes \ alleles \ interpretation

An over - simplification

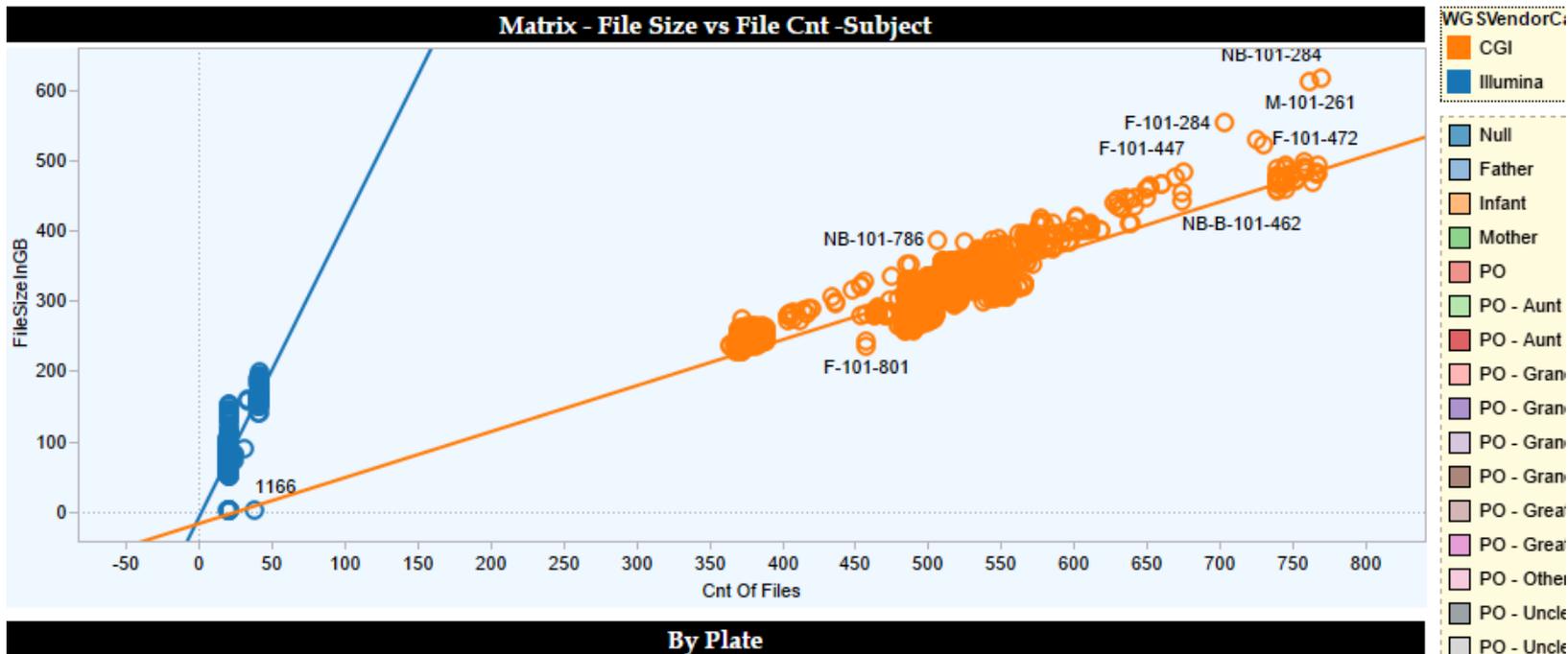
	Simple	Complex	Structural (Insert)
REF	A T T G C T	A T T G C T A T T G C A	A T T G C A T A C G C A T T G C
ALT	A A T G C T Blue	A A T G C T A T T C G A Blue + Yellow	A T T C G A T A C G C A A T G C Yellow ??? Blue
		Call it Green or (Blue + Yellow)? What if there is a 3 rd \ 4 th or \ 5 th color?	What do you call this? What if there is 10 digits between these sequences? Do we change what we call it?

B High Confidence Drivers (HCDs) detected by each method



- Standardization of Metadata
 - Platforms
 - NGS \ Microarray and other
 - Depth, quality
 - Annotation
 - Lack of standard knowledgebase
 - Open Source vs. Proprietary
 - Lack of Vendor Incentive
 - To conform to standard
 - Or provide standard messaging
 - Analysis Software
 - Output differences
 - Differences in interpretation (quality and refresh rate of knowledgebase)
 - Filtering \ Versioning

- Output differences – examples -> Whole Genome Sequencing



More Variation – Variant Count Differences

Illumina		Complete Genomics	
Sample ID	Variant Count	Sample ID	Variant Count
M-101-782	30,852,475	M-101-860	21,730,706
M-101-745	30,042,376	M-101-859	22,608,801
M-101-739	26,707,715	M-101-857	21,799,979
M-101-738	30,129,628	M-101-853	22,107,158
M-101-725	29,824,009	M-101-852	21,716,404
M-101-564	31,643,799	M-101-844	23,669,638
M-101-563	29,468,614	M-101-841	22,096,639
M-101-552	30,168,363	M-101-840	22,839,358
M-101-551	42,026,951	M-101-831	24,769,292
M-101-545	37,007,718	M-101-822	22,556,401
M-101-541	31,025,564	M-101-809	24,125,402
M-101-533	28,782,119	M-101-807	23,466,095
M-101-531	32,470,193	M-101-803	26,707,844
M-101-527	26,249,287	M-101-798	23,277,692
M-101-521	27,790,222	M-101-797	24,547,830
M-101-520	36,558,146	M-101-792	22,092,334
M-101-515	35,030,081	M-101-791	
M-101-514	29,651,471	M-101-783	
M-101-513	29,048,264	M-101-782	
M-101-512	32,646,148	M-101-777	
M-101-511	31,727,054	M-101-768	

select sample_id, COUNT(*) as cnt
 FROM vcf_variant
 group by sa

Variant Rows\ Variant File		
Avg Illumina	Avg Complete Genomics	Pct Difference
37,891,953	22,983,258	39%

Variant Rows\ Variant File			
Avg Illumina	Avg Complete Gen.	Totals	
37,891,953	22,983,258		
Genome Numbers	5,501	2774	8,275
Variant Rows	208,443,630,919	63,755,558,741	272,199,189,660
Variant Row Columns	27	27	54
Total Data Points Tracked	5,627,978,034,812	1,721,400,085,999	7,349,378,120,811

- Constantly new and updated information on current genes \ molecular markers
 - Standardization is crucial for constantly updating knowledge base
 - In order to realize value, providers and vendors need to keep knowledge updated
 - Mechanisms to alert patients of new information
 - Legal and ethical considerations
 - Business \ how long to keep data?
 - What results to return?
 - Clinically Actionable
 - Variants of unknown significance
 - Other?
- Other items to consider
 - How long to store raw and intermediate results? Which results? Costs?
 - How often should we update the knowledge base? Upon request, will it be a billable service?
 - Should we scan records when there is a major adverse discovery found?

Genetic \ Genomic Test

Gene

Variant \ Allele

Interpretation

- PGx Panel test example
 - LOINC code: **55208-3** - DNA analysis discrete sequence variation panel
 - <http://r.details.loinc.org/LOINC/55208-3.html?sections=Comprehensive>
 - Gene:
 - LOINC code: **48018-6** - Gene Identifier
 - <http://r.details.loinc.org/LOINC/48018-6.html?sections=Comprehensive>
 - *Human Genome Organization Nomenclature Committee Identifier for a Genes*
 - Allele
 - LOINC code: **53034-5** - Allelic state
 - <http://r.details.loinc.org/LOINC/53034-5.html?sections=Comprehensive>
 - *Heteroplasmic* LA6703-8
 - *Homoplasmic* LA6704-6
 - *Homozygous* LA6705-3
 - *Heterozygous* LA6706-1
 - *Hemizygous* LA6707-9
 - Interpretation
 - LOINC code: **53040-2** - Drug metabolism sequence variation interpretation
 - <http://r.details.loinc.org/LOINC/53040-2.html?sections=Comprehensive>
 - *Ultrarapid metabolizer* LA10315-2
 - *Extensive metabolizer* LA10316-0
 - *Intermediate metabolizer* LA10317-8
 - *Poor metabolizer* LA9657-3

Genetic \ Genomic Test

Gene

Variant \ Allele

Interpretation

Genetic \ Genomic Test Panel

Gene

Variant \ Allele

Interpretation

Gene

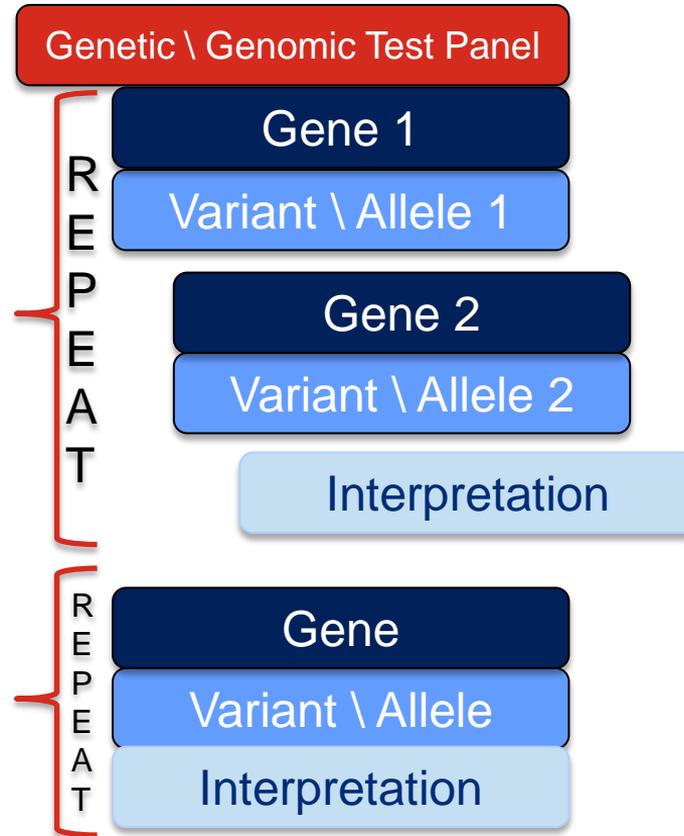
Variant \ Allele

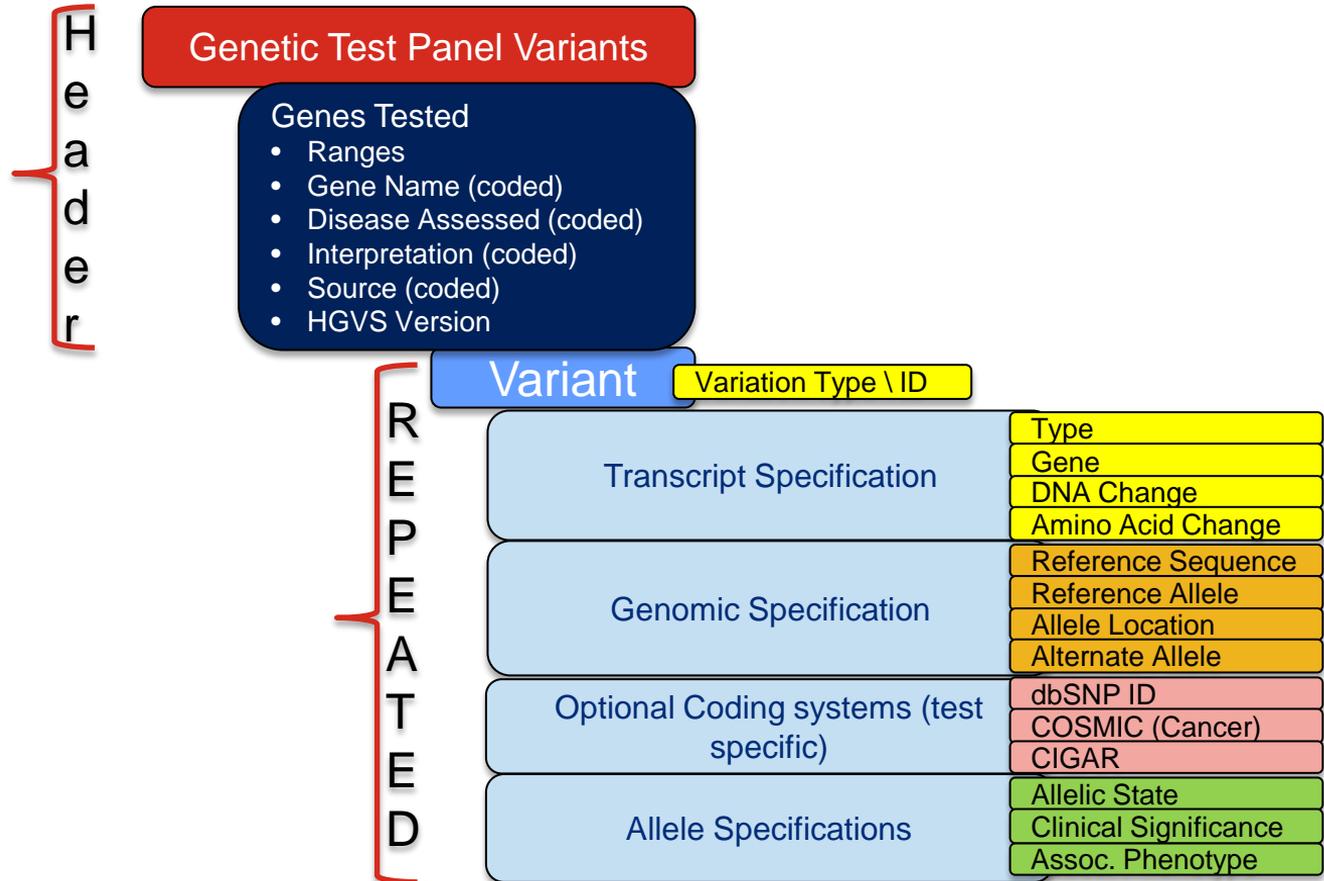
Interpretation

Gene

Variant \ Allele

Interpretation





Genetic Test Panel Variants

Genes Tested

Simple Variant

Transcript Specification

Genomic Specification

Optional Coding systems (test specific)

Allele Specifications

Complex Variant

Simple Variant

Transcript Specification

Genomic Specification

Optional Coding systems (test specific)

Allele Specifications

Simple Variant

Transcript Specification

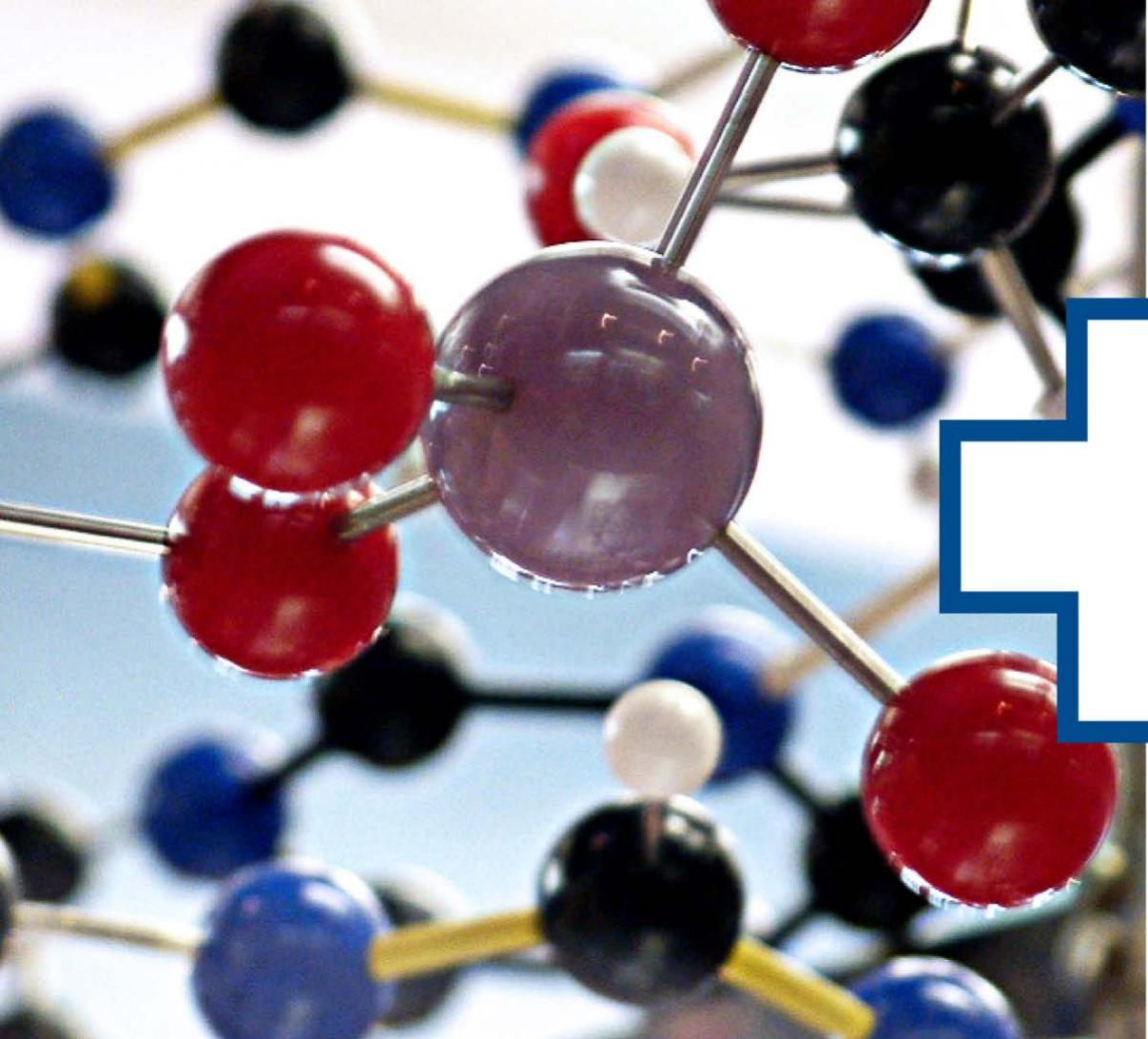
Genomic Specification

Optional Coding systems (test specific)

Allele Specifications

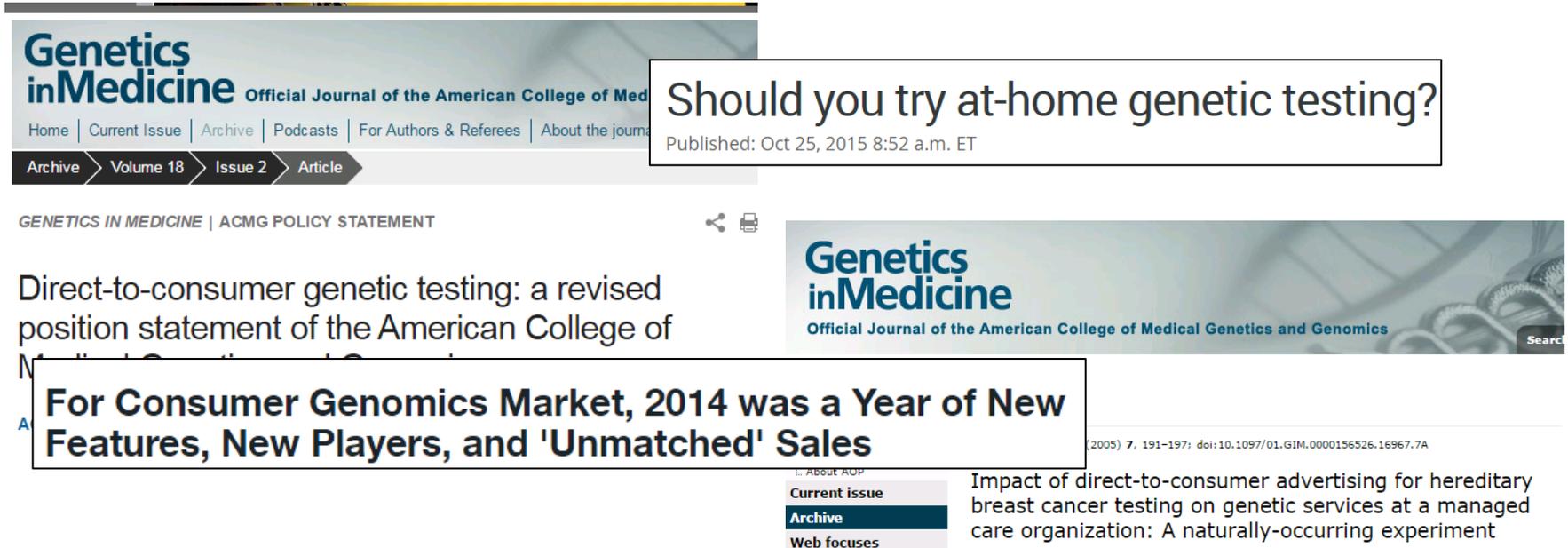
Structural Variant

All Can Repeat



Opportunities

- **Consumer demand**
 - Consumers are demanding genetic and genomic interpretations



The screenshot shows the top portion of a web page for the journal *Genetics in Medicine*. The page title is "Should you try at-home genetic testing?". The journal's logo and name are visible in the top left. A navigation bar includes links for Home, Current Issue, Archive, Podcasts, For Authors & Referees, and About the journal. Below the navigation bar, the article title is highlighted with a white box. The publication date is "Published: Oct 25, 2015 8:52 a.m. ET". Below the article title, there are social media sharing icons. The page also features a secondary header for "Genetics in Medicine" with the subtitle "Official Journal of the American College of Medical Genetics and Genomics". A search bar is visible on the right side of this header. Below the header, the text "GENETICS IN MEDICINE | ACMG POLICY STATEMENT" is displayed. The main content area begins with the text "Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics". Below this, another article title is highlighted with a white box: "For Consumer Genomics Market, 2014 was a Year of New Features, New Players, and 'Unmatched' Sales". At the bottom of the page, there is a navigation menu with options: "I. ABOUT AGP", "Current issue", "Archive", and "Web focuses". The "Archive" option is currently selected. To the right of the navigation menu, there is a snippet of text: "Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: A naturally-occurring experiment".

Should you try at-home genetic testing?
Published: Oct 25, 2015 8:52 a.m. ET

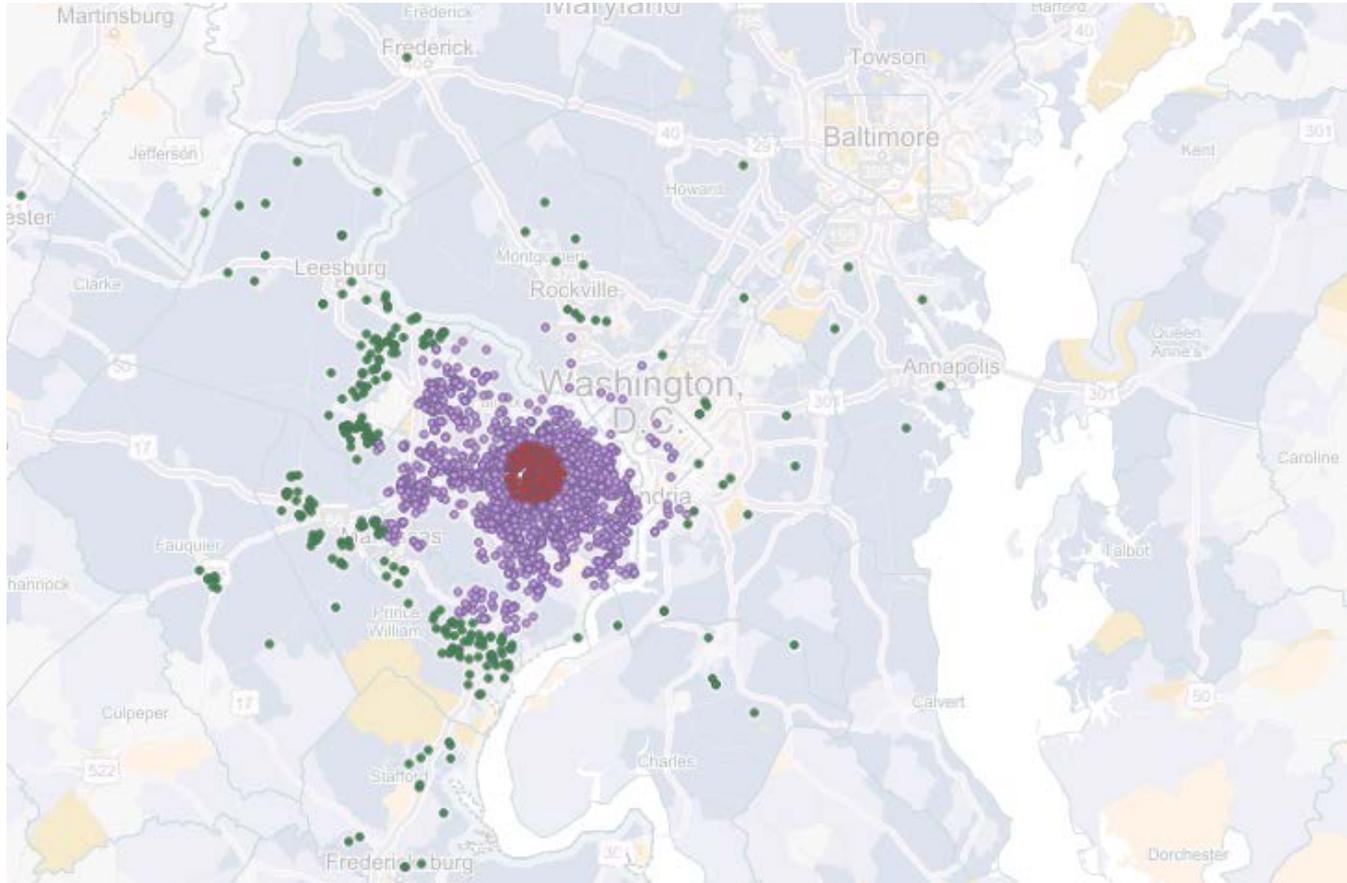
GENETICS IN MEDICINE | ACMG POLICY STATEMENT

Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics

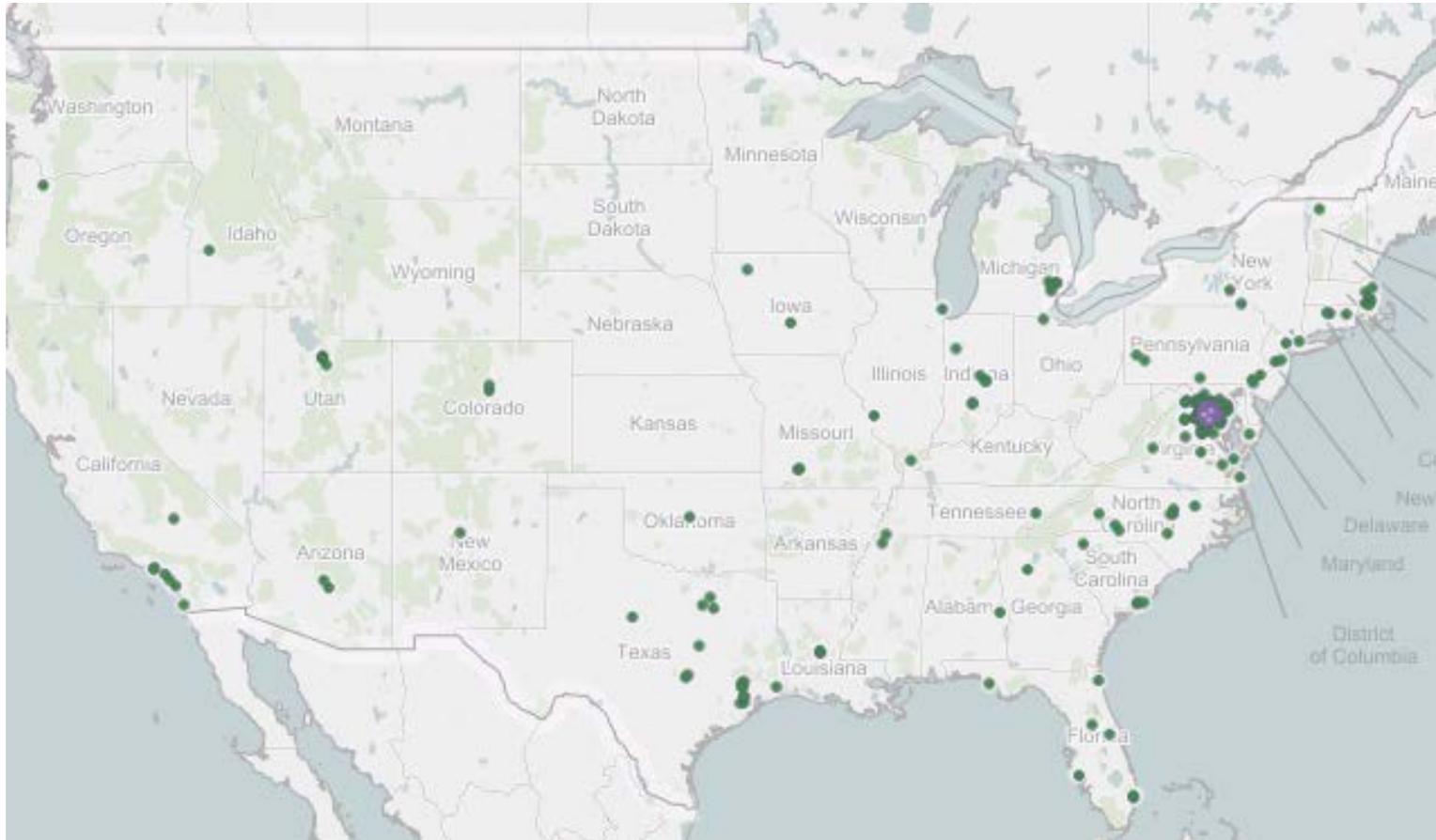
For Consumer Genomics Market, 2014 was a Year of New Features, New Players, and 'Unmatched' Sales

Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: A naturally-occurring experiment

Transient Population - Example



Transient Population - Example



- Movement to Proactive Health Management
 - Personalized, Preventive, and Precise
 - Focus on specific risks in specific patients
 - Increase surveillance of high-risk individuals
 - Able to use high-risk medications for targeted individuals
 - Reduce adverse events in high-risk individuals
- Improved Clinical Decision Support
 - Timely application of new genomic knowledge in delivery of healthcare
- Reduced Health Care Costs
 - Reduced adverse events
 - Decrease potential liability

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U.S. HEALTH IN INTERNATIONAL PERSPECTIVE

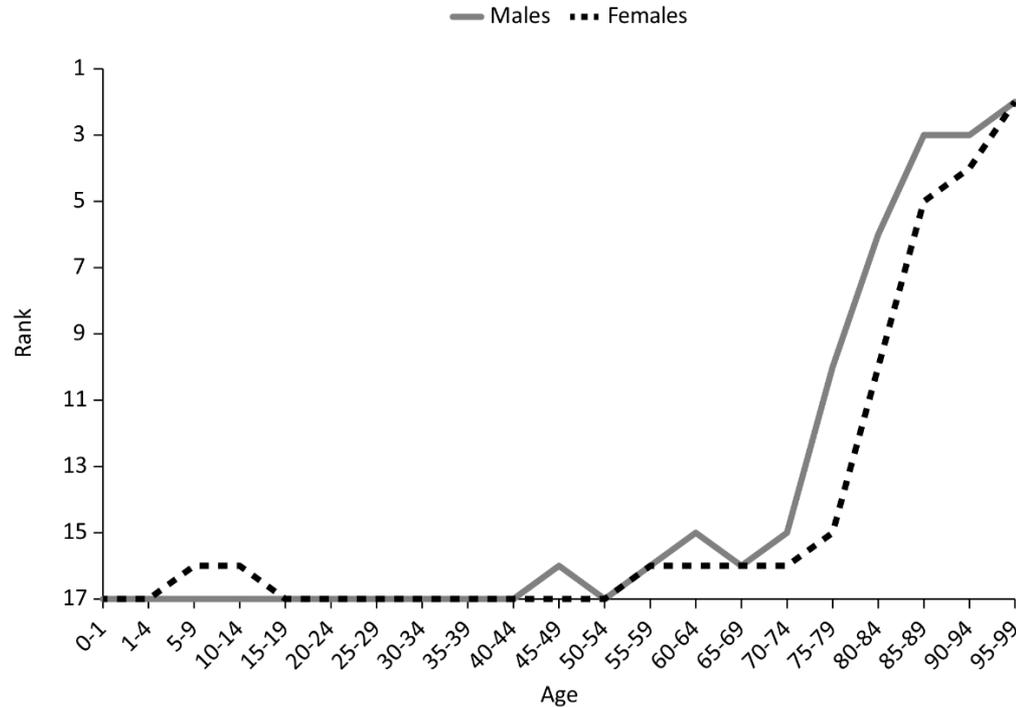


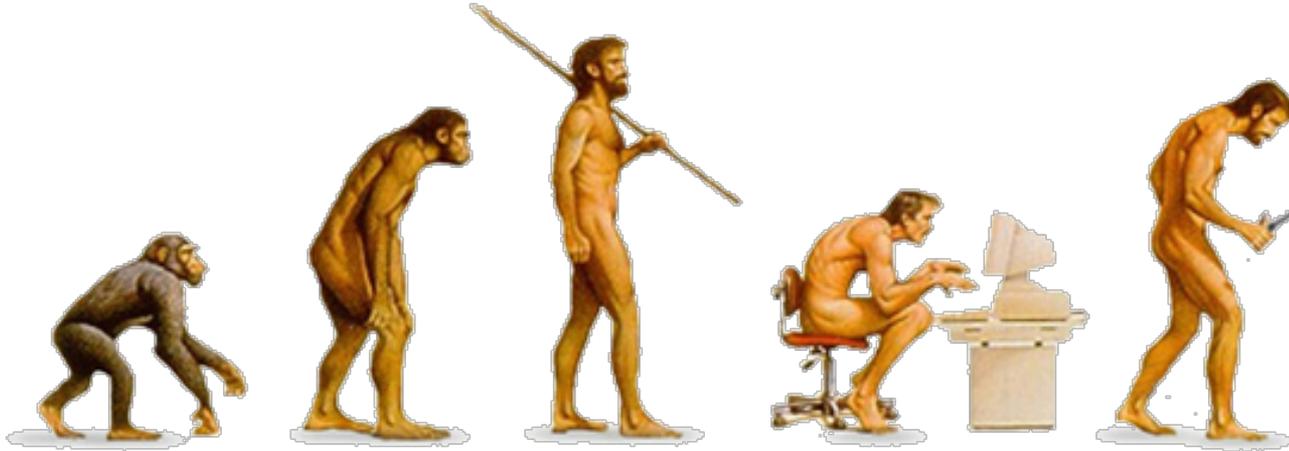
FIGURE 1-9 Ranking of U.S. mortality rates, by age group, among 17 peer countries, 2006-2008.

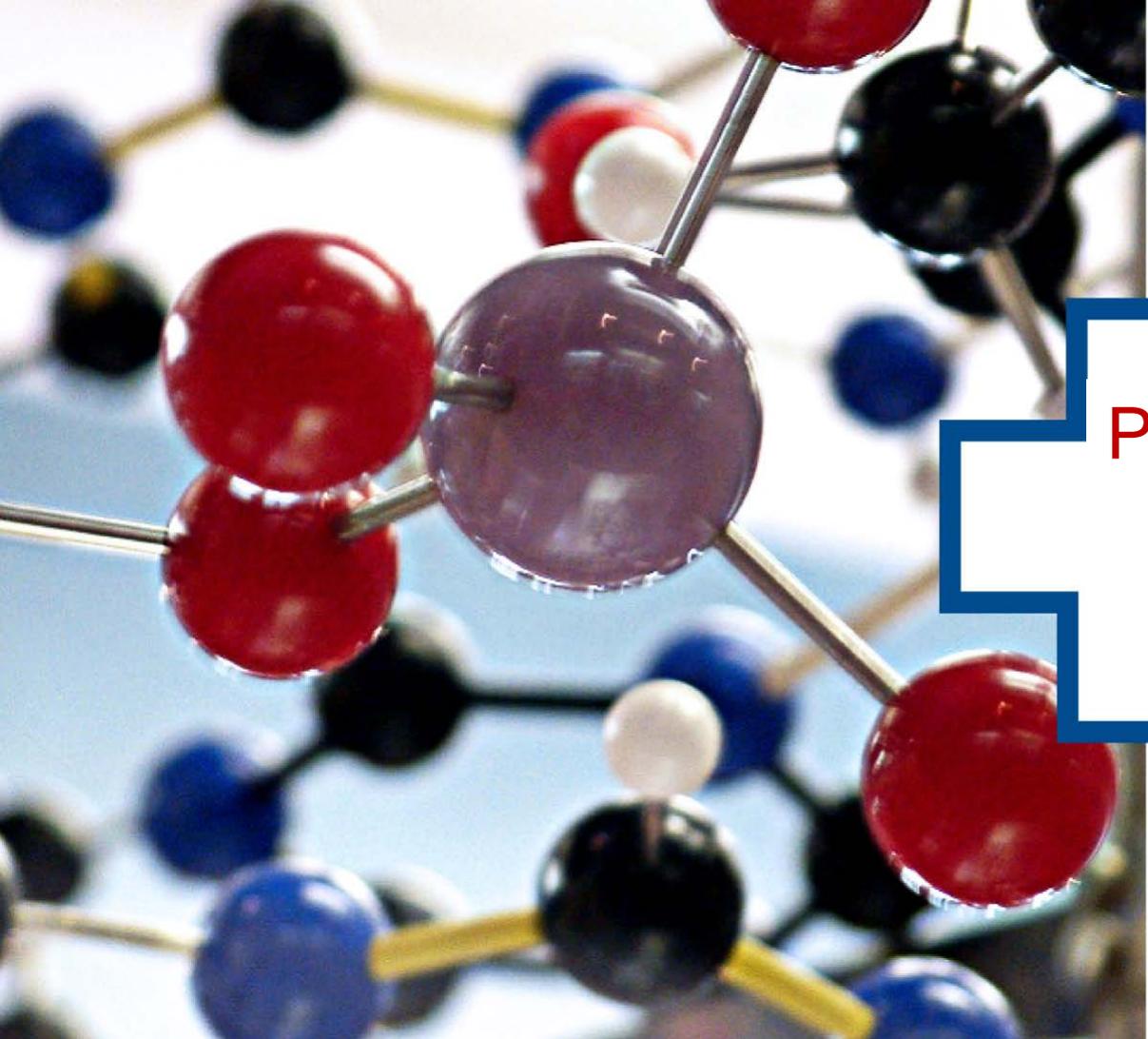
- Cost savings
 - Tests can be run once
 - Save costs to reinterpret vs new test and analysis
 - Computer and staff time savings
- Further savings if this data can be securely exchanged between institutions
- Utility grows exponentially as more data and information is gathered
- Create standardized methodology for Return on Investment (ROI)
 - Benchmark for institutions who are evaluating tests
 - Used to help drive reimbursement from Government and Private Insurance

- Become US leader in genetic \ genomic testing standards
 - Attractive to partnerships and opportunities both inside \ outside of Virginia
- Research
 - Consortium of Virginia institutions and collaborators can produce high quality, consistent and large datasets for research and collaboration
 - Population Health – genetic \ genomics results combined with other healthcare datasets
 - Collaborations for research and technology development
 - Private \ Public partnerships and investment
- Virginia can attract and keep people and families who value the best healthcare
- Attract health, scientific and technology talent to work in Virginia
 - Work with software and data companies for mutual benefit
- Venture Capital and Philanthropy
- Advise other State and Federal Agencies

- **Momentum**
 - Large push from Government, Academia, Venture and Philanthropy
- **Consortium**
 - Group think, others are pushing forward and provide valuable information.
- **Optimizations**
 - More knowledge of costs and performance metrics for better evaluations of studies and clinical testing.

- **Vendor Maturity in Healthcare and Life Sciences**
 - Many more valid options, more understanding and less ramp-up time.





Proposed Process for Genetic \ Genomic Standards

- Current Implementation Roadmap Recommendations (used by several pilot organizations)
 1. Incorporate design in databases
 2. Implement design standard in laboratory reports and/or data files
 3. Validate utility of information model through active use in business
 4. Iterate on information model incorporating lessons learned
 5. Formally develop HL7 interfaces for fully codified/qualified data when business is ready

- **Proposed process**

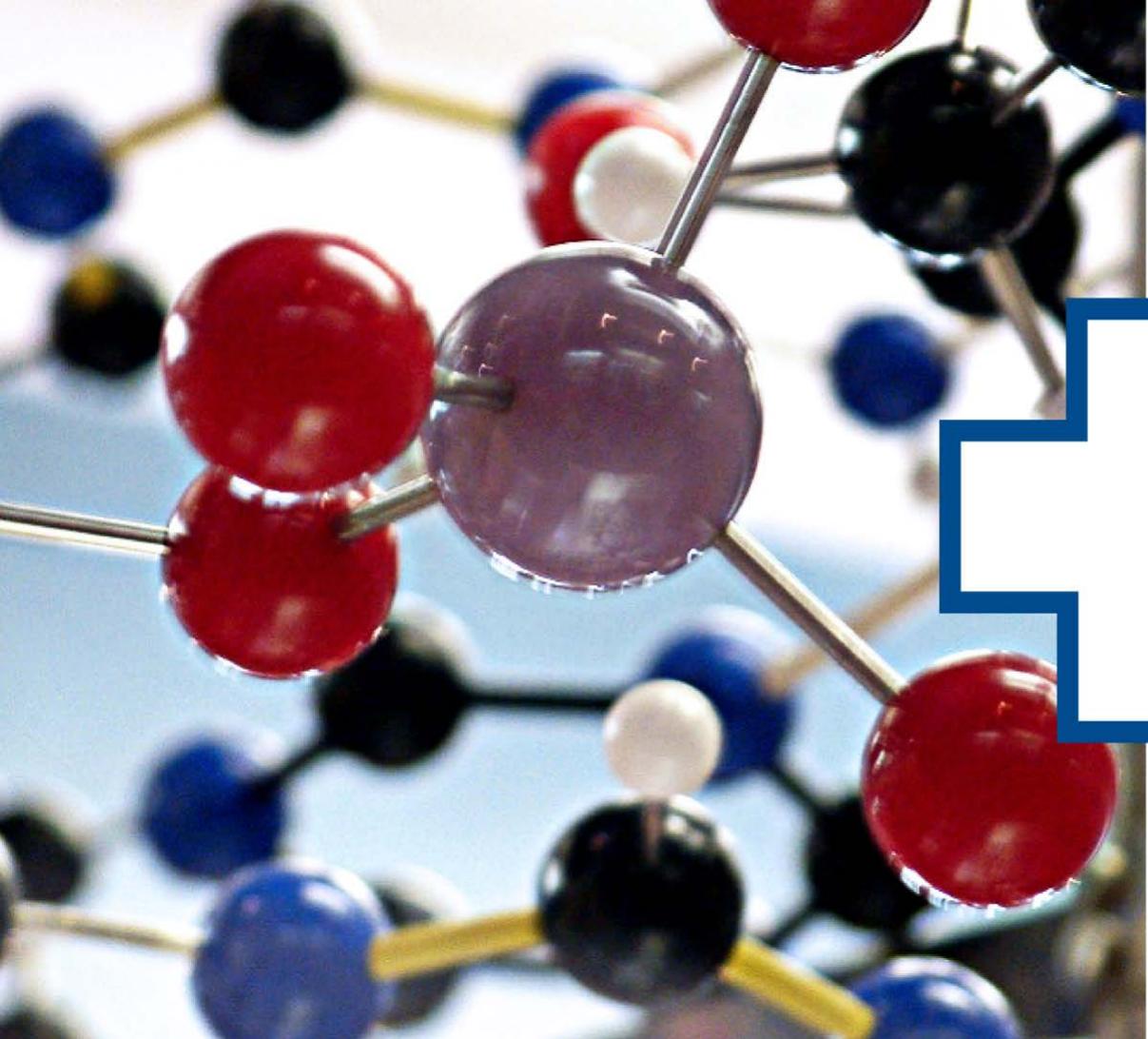
- (1) Organize cross functional team to build methodology on data specifications for Genetic and Genomic tests
- Who?
 - Hospitals \ State Labs (2-3 distinct institutions)
 - Criteria
 - » Have or will offer genetic \ genomic tests
 - » Lab \ Genetic Experts (humans, microbes, animals)
 - » Dedicate Clinical, Genomic and EHR expertise
 - » Informatics experts
 - Virginia Government
 - External informatics experts (HL7 and LOINC)
 - Software vendor(s)

- (2) Goal for cross functional team
 - Create standards recommendations to Virginia for at least 2 genetic tests
 - Select:
 - One simple test
 - One slightly more complex
 - An example would be Pharmacogenomics (PGx)
 - Simple → Individual Gene \ Drug test (ie Plavix)
 - More complex → Set of PGx genes and alleles

- (3) For those tests, the team would present specification to HITSAC recommendations on, but not limited to the following:
 - Coding and messaging standards (LOINC, HGVS, COSMIC..)
 - Data exchange standards between like institutions (LOINC..)
 - Reporting standards
 - Return of results to EHR (Formats and exchange \ LOINC, HL7)
 - Impact of tests
 - » Patient care improvement (short and medium term)
 - » ROI
 - » Overall Efficiencies gained

- (3) Present roadmap for future tests to evaluate standards for more complex and diverse tests.
 - To support clinical use cases like:
 - Newborn screening
 - Prenatal screening
 - Cancer treatment \ Clinical trials \ Cancer Registry
 - Rare disease
 - Public Health Reporting \ Virginia Health Information Exchange
 - Type of tests \ technologies
 - Panels - NGS \ Array and others
 - Whole Exome and Genome
 - Proteomics \ Cytogenetic testing

- Complex standards need experts from multiple disciplines
- Agility will be key, as tests and national standards adopted \ change
- Start with simple tests. The standards are better defined for the simple tests
- Application of these standards in one or more institutions will help filter out real world issues and create momentum.
- This is needed (period).



Q&A

Comments

Inova Translational Medicine Institute

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Joe Vockley PhD

Ben Solomon MD

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Ram Iyer, PhD

Dale Bodian, PhD

Wendy Wong, PhD

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Dr. Ryan Bosch and Team

Jeannie Brooke and Team

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and teams