Considerations when launching a Genome Wide Sequencing based MDx test

Liz Worthey Ph.D.
Assistant Professor; Department of Pediatrics, MCW
Director; Genomic Informatics, Genomic Medicine Program, Human and Molecular Genetics Center, Medical College of Wisconsin
Faculty; Children’s Research Institute, Children’s Hospital of Wisconsin
Director, MCW-Marquette Bioinformatics MSc program
Faculty; Department of Computer Science, UW Milwaukee
Co-Founder Genomic Healthcare Innovations
@lizworthey
Mid sized Regional Medical Center in Southeastern Wisconsin Children’s Hospital, Adult hospital, and regional VA hospital care for ~450,000 patients, representing ~1.6 million patient visits per year.
Started out as the HMGC sequencing core lab; ABI, 454, Illumina

Entry into Clinical genome wide sequencing (exome) at the end of 2009
MCW/CHW GWS based pilot now Genomic Medicine Clinics

Genomic Medicine Clinic

The Genomic Medicine Clinic at Children’s Hospital of Wisconsin (CHW) in collaboration with the Medical College of Wisconsin (MCW)/Children’s Hospital of Wisconsin and Molecular Genetics Center at the Medical College of Wisconsin, provides medical evaluation, pre-test education, genome sequencing, report generation and review, clinical interpretation and review, and ongoing care.

Our team of experts were one of the first in the nation to utilize NGS to diagnose and treat a previously undiagnosed genetic condition. Click here to learn more about the story. Our experts view genetics as a powerful diagnostic tool and use a multi-step refined process for education, analysis and ongoing care.

Genomics in the news

Cracking your genetic code
Advancements in genetic testing
DNA sequencing leads to diagnosis and treatment
Genomic Healthcare Innovations

- Clinical Whole Genome & Exome Sequencing
- Targeted Panels
- Robust Cutting Edge Analysis & Interpretation
- Hands on Knowledge of Use in Care; Training for Use
- Stat TATs Possible; Ongoing Optimization

Genomic Healthcare Innovations (GHI) is a genomic diagnostics company that uses results from clinical genomic sequencing to guide the care of patients. Through the CLIA-certified clinical sequencing laboratory at the Medical College of Wisconsin (MCW), GHI offers clinical whole exome, whole genome, gene panel and Sanger sequencing testing as well as clinical genomic sequence data analysis and interpretation using our proprietary bioinformatics platform, CarpeNovo.

Genomic Healthcare Innovations, LLC  www.genomici.com  MCW Sequencing Laboratory CLIA# 52D104336
WHAT INFORMATICS AND IT INVESTMENT WILL BE REQUIRED TO REACH CLINICAL GRADE HIGH THROUGHPUT?
In house informatics applications

CarpeNovo

GapMine

Psyche

Sample accessioning and report tracking

WindowPath

Extraction through sequencing

Demultiplex through mapping & alignment

BWA-MEM

GATK HC

In house automation & QC

Report generation and sendout

Post tertiary and Clinical interpret’n

Variant annotation and analysis preparation

Variant calling and QC analysis

Extraction through sequencing

Storage

LIMS

Applications

In house informatics applications

ClinMiner

OntoMate

HDO HPO Integration
Where are the bottlenecks?

• The sequencing and primary analysis is (relatively) easy
  – Works sufficiently well and can be scaled to support accurate high throughput clinical sequencing of a genome

• The secondary analysis is (relatively) easy
  – Many competing solutions
  – We found BWA-mem/GATK HC to work well
  – A little slow, but works sufficiently well and can be scaled to support accurate clinical high throughput

• The tertiary analysis is now (relatively) easy
  – Various solutions work pretty well
  – Can be scaled to support accurate high throughput so long as you have a robust platform in place

• The post tertiary analysis / interpretation / reporting phase contains the most significant bottlenecks
  – A few solutions; most not clinically oriented
  – The slowest, most expensive, least robust, least expandable, and most error prone part of the process
Selecting appropriate analytical tools

Comparison of variant calls

- ALL: 74.09%
- GATK: 8.53%
- Casava: 8.14%
- GATK & Casava: 2.54%
- Isaac: 2.10%
- GATK & Isaac: 2.48%
- Isaac & Casava: 2.12%

Initial concordance between pipelines is somewhat low
But stringently applied quality filtering dramatically increases concordance

### Participant Summary

Sample Exchange Registry for Alternative Assessment for Exome/Genome Sequencing (ES/GS)

2014-A Mailing

<table>
<thead>
<tr>
<th>Participating Laboratories</th>
<th>Specimen</th>
<th>Method</th>
<th>Caller</th>
<th>Target SNPs</th>
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Current informatics workflow

Workflow automation including QC modules

QC data gathering
- QC checkpoints

Clarity Lab Information Management System

Mapping
- BWA-mem v 0.7.7
  - Read mapping

Post Mapping
- SAMtools v 1.1: Fixmate, sort, & index
- Picard v 1.108: Mark duplicates
- GATK v 3.2.2: Realign and recalibrate

Variant Calling
- GATK-HC v 3.2.2
  - Substitution, Insertion, Deletion calling

Coverage
- GapMine v 3.1.0
  - Gene, Transcript, and Exon coverage

Annotation & Prioritization
- CarpeNovo v 5.2.0
  - Variant annotation and Prioritization

Interpretation & Reporting
- CarpeNovo v 5.2.0
  - Support for interpretation and clinical report generation

Additional QC analysis and review

Sanger confirmation

>95% automation
With an appropriate interpretation process and tools review is efficient

4 step process, times for WGS:

• Precomputation of annotations and prioritization (~5-10 mins ave.)
• Clinical analyst review of prioritized variants (~1 hour ave.):
  – Are variants identified through our algorithms likely real or likely errors?
  – Is the GxP reported relationship reliable or not?
  – Is the data sufficient quality for clinical reporting?
  – Analyst adds additional annotations and comments based on review
• Director interpretation (~1 hour ave.)
  – Rapid review of analysts findings
  – Additional analysis of candidate variants as required/desired
  – Going off the reservation can extend this time; some directors enjoy this activity more than others
• Report generation, review, sign off, and send out (15 mins ave.)
  – Variants selected for reporting are sent for Sanger confirmation
Considerations

INITIAL 1/3 FTE (OVER 6 MONTHS) INVESTMENT IN THE WRITING OF DOCUMENTATION
Applications must meet validation, certification, and documentation standards

Certified and compliant: to meet federal quality and proficiency standards.

Accredited: to meet required Educational, Proficiency, Methodology, Quality and QC standards.

>400 pages of informatics/IT SOPs (41 distinct SOPs)
Validation following a change or new release is a significant task
Maintenance of documentation is a significant task
Considerations

WGS, WES, OR PANELS?
There is a bias in the way gene to disease symptom associations are created

1. A Clinical Presentation $\rightarrow$ Causal Gene relationship is likely to be set up based on identification of deleterious molecular changes in one or a small number of individuals with a shared phenotype.

2. Subsequently, that gene will be tested for variants in patients with that same or a very similar clinical presentation.

3. Leaves no room for unusual or alternative presentations, pleiotropic effects.

4. If you only look at genes (single or panels) already associated with your patients phenotype you might miss the answer; sometimes it is an easy answer.

5. WGS & WES have the power to uncover such unexpected findings.
Example; Nic

- Presented 18 months with poor weight gain and a perianal abscess
- Symptoms progressed rapidly to an unusual early onset, aggressive, refractory inflammatory bowel disease
- In spite of aggressive therapy disease continues to progress
  - Immunosuppressants
  - Diverting colostomy at 2 years
    - Notably poor wound healing
  - Total colectomy then partial ileostomy at 4, ongoing immunosuppression
  - Complete bowel rest at 4.5 years
- Host of diagnostic tests performed
- No diagnosis – no way forward
- Is this an immune defect?
- Immune reconstitution?
- Clinical WES performed 2009
WES identifies the causal mutation

- Genomic locus Xq25 - XIAP
- G>A, p.C203Y change
- Hemizygous, Novel, Inherited
- Important in termination of damaged, infected, or aberrantly performing cells; immune system development

Reference

Patient

Mother

Development of assays to test patients immune response to pathogens, NOD signaling
- Confirmation of defective XIAP pathway signaling
- Diagnosed with functional defect in XIAP protein
- Causing immune dysregulation resulting in IBD
- Cord blood transplant led to cure
WES led to XIAP deficiency diagnosis, but...

• XIAP had been a known disease gene since 2006; so why wasn’t he diagnosed earlier?
• XIAP had not been associated with colitis... only XLP2

• But, after our publication linking XIAP with colitis:
  - Schmid ‘11 - 17% of XLP2 patients had chronic hemorrhagic colitis
  - Speckmann ‘13 - 6/25 XLP2 patients suffer from severe Crohn-like bowel disease – in some cases leading to death
  - Zeissig ‘14 - deleterious variants in XIAP in ~4% of 274 male patients with paediatric-onset CD

• If we had used a panel of 2,000+ genes we would not have made the diagnosis

• But we were able to find it with WES
So.... Genome wide sequencing is better than a panel, but WGS is better that WES; it is the best first test

• Used to arguably be too expensive
• But Illumina’s HiSeqXs drastically reduce the cost
  – Providers now offering HiSeqX WGS for around ~$1,500 US
  – Of course not everyone has a HiSeqX, but they will have it or an equivalent technology in the near future once Illumina saturates the initial 10X ~$10million market 😊
WGS can provide more and better quality data for diagnostics

• WES precludes ability to interrogate ~98.5% of genome
  – Some non genic regions are known causal loci and easy to interpret
  – We have identified a pathogenic 5’UTR variant that would not have been ID’d through current WES methods

• WES excludes many exonic regions
  – We have identified pathogenic protein coding & splice variants that would not have been seen through current WES methods because they were not targeted as clinically actionable genes

• WES coverage is more variable over the exome
  – 40x coverage WGS covers 96% of exome at 20x compared with 85% from a 100x exome – MCW and Garvan Institute findings
  – WES risks missing important regions due to capture variability
And... some commonly stated limitations of WGS in the clinic are overstated

• Clinical interpretation of WGS data no harder than WES
  – Most of the genome is not interpretable
  – But some is!

• Analysis and clinical interpretation of WGS derived data does not take significantly longer than WES data

• Analysis and interpretation of WGS derived data does not require more sophisticated interpretation tools as compared to WES

• Pending formal decisions around long term data storage it isn’t clear that it will cost significantly more to store WGS derived data though currently it does; and can be a cheaper storage solution
Considerations

TAT
Current TAT offerings

- Standard WGS or WES test - 90 day TAT
- STAT WES or WGS test - 14 day TAT
- Current most rapid turnaround has been 5 days from samples receipt to return of findings
Considerations

YOU CANNOT RELY ONLY ON DATA FROM MUTATION DATABASES FOR INTERPRETATION
Example - Lilian

- 4 year old ex 30 week preemie
- Pregnancy complications:
  - IUGR, oligohydramnios, and maternal Hemolysis,
    Elevated liver enzymes, and Low Platelets
  - syndrome, preeclampsia, and elevated BP
- Following emergent C section:
  - Failure to thrive, chronic diarrhea, and VSD
- NICU for 3 months:
  - Episodes of sepsis, *S. aureus* and *enterobacter*
  - Failed hearing exam: Stenotic right ear canal; Atretic left ear canal
  - Periods of neutropenia, thrombocytopenia, low hematocrit
- Unusual hair texture
- Extensive evaluation
  - Many institutions and specialties: GI, Genetics, Immunology
WGS: 1 ultra rare premature stop, 1 novel splice site in SKIV2L

Nucleotide change

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Amino acid change

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rRNA processing ARCH domain
DSH C-terminal domain
Helicase domain
P-loop nucleoside triphosphate hydrolase domain
Helicase superfamily 1,2 ATP-binding domain

cDNA analysis shows that introduction of the variant impacts use of the constitutively used splice site with:
- Use of an **upstream** splice site in ~1/3 of this copies transcripts.
- **Incorporation** of the nucleotides and amino acids in yellow.
- Leading to a frameshift and formation of a premature stop.
Putative human SKI complex

Roles:
• 3' degradation of mRNAs
• Guidance of mRNAs to the exosome for degradation
• Additional postulated role in cellular growth and division

• Associated with Trichohepatoenteric syndrome 1 (THE1)
  • A rare congenital bowel disorder with chronic diarrhea, intrauterine growth retardation, and hair and sometimes facial abnormalities.
• TTC37/THE1 previously considered, tested, and excluded.
SKIV2L literature in February 2012

• Nothing in OMIM
• Nothing in mutation databases e.g. HGMD
• 13 PubMed papers
  – Potential association with age-related macular degeneration and recurrent sub-retinal and sub-retinal pigment epithelium bleeding
  – Sex-specific childhood leukemia risk
• An interesting connection but insufficient evidence for clinical reporting up to this point
• Variants annotated as likely deleterious to function, but gene was and remains a GUS
• No diagnosis...
SKIV2L mutations cause syndromic diarrhea, or trichohepatoenteric syndrome.

UMR_S 910, Inserm-Faculté de Médecine, Aix-Marseille Université, Marseille, France.

Abstract
Syndromic diarrhea (or trichohepatoenteric syndrome) is a rare congenital bowel disorder characterized by intractable diarrhea and woolly hair, and it has recently been associated with mutations in TTC37. Although databases report TTC37 as being the human ortholog of Ski3p, one of the yeast Ski-complex cofactors, this lead was not investigated in initial studies. The Ski complex is a multiprotein complex required for exosome-mediated RNA surveillance, including the regulation of normal mRNA and the decay of nonfunctional mRNA. Considering the fact that TTC37 is homologous to Ski3p, we explored a gene encoding another Ski-complex cofactor, SKIV2L, in six individuals presenting with typical syndromic diarrhea without variation in TTC37. We identified mutations in all six individuals. Our results show that mutations in genes encoding cofactors of the human Ski complex cause syndromic diarrhea, establishing a link between defects of the human exosome complex and a Mendelian disease.

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- Lilian diagnosed with THE2
- No cure, but an answer and information to guide care; testing and monitoring for potential syndromic abnormalities such as cardiac abnormalities and progressive liver disease
But say we didn’t have the Fabre paper

• 2012  
  - Lilian’s likely deleterious variants in SKIV2L GUS identified

• 2013  
  - 2 additional unrelated patients with IUGR, chronic diarrhea, & unusual hair found to have likely deleterious SKIV2L variants

• 2014  
  - 2 additional unrelated patients with IUGR, chronic diarrhea, & unusual hair found to have likely deleterious SKIV2L variants

• Because we interrogated genome wide we could well have made a diagnosis in 2013 based solely on data  
  - Despite the fact that SKIV2L would not have been on any clinically actionable gene panel at that point in time  
  - But only because we found additional patients in our cohort
Really useful to be able to find other similar (G and P) patients elsewhere

Months for this data to be gathered and published. Many months to get the data into disease databases..... far too slow...

You need tools to share genomic and clinical presentation data across labs

Not simply as a central repository; ideally on the fly sharing

Some progress in this area recently supporting lab to lab sharing

Current estimates are that there are >50 new disease associations ID’d per month
Considerations

YOU NEED TO BE VERY CAREFUL ABOUT THE REFERENCE DATA YOU USE
RYR2 and ARVD/CPVT

- Heterozygous for Ryanodine receptor 2 (RYR2) p.G1885E
- Pathogenic variants in RYR2 associated with:
  - Sudden Cardiac Death (Autosomal Dominant ARVD & CPVT)
  - Estimated prevalence of 1/20,000 in the United States
  - ~30% of cases affected at ≤40 year of age
- p.G1885E is categorised as a known pathogenic variant (data from 4 independent high quality studies)
- No history or confirmed family history
- But, father drowned in his late 30s
Pathogenic or?

• 4 papers conclude it is pathogenic
• But combining the datasets from the cohort analysis papers we see:
  – Het p.G1885E has similar frequency in controls and patients:
    – 41/761 patients (5.4%) are Het p.G1885E
    – 76/1,495 controls (5.1%) are Het p.G1885E
• 2011 paper
  – Identified Het p.G1885E as the pathogenic variant in an ARVD patient
  – But from info in supplemental table patient also additional previously published pathogenic variants in another ARVD gene
• And prevalence of p.G1885E in large recently datasets found to be:
  – 1.5 - 6% in Caucasian, African American, and Han Chinese cohorts
• So actually a not very rare polymorphism
• Careful QC of reference data required
Considerations

IS THERE ANY NEED TO SANGER CONFIRM?
Sanger confirmation is probably still required; especially at the start of your process

- We continue to Sanger confirm everything
- 1.2% of variants have not Sanger confirmed
  - Has improved over time
- Sanger confirmation is absolutely required for:
  - All low-quality single-nucleotide substitutions
  - All small insertions, deletions, and indels
Considerations

SHOULD WE USE A GENE LIST FOR REPORTING OF SECONDARY FINDINGS OR NOT; PERHAPS ACMG LIST?
Comparison of what we have reported versus ACMG gene list

• Only 5.6% of our cases have been reported with pathogenic or likely pathogenic variants in genes in the ACMG incidentals gene list
• 67.8% of the genes we have reported on are not in the list
• Most (87.5%) of the ACMG genes did not show up
• Many patients would not have received what our clinical team deem to be medically useful information if we had limited to this gene list
FINDINGS
“Success rate”

- The pre NGS “Standard of care” Molecular Diagnostic Testing success rate for cases in the care of a Clinical Geneticists was anecdotally ~10%.
- With WES or WGS we return clinical findings in ~35% cases.
- We find WGS is better than WES (~5% more diagnoses)
- But these early cases were not the easiest cases; if we used as a first line test (not that we should just yet) WGS would undoubtedly have a significantly higher success rate (80%?)
- In a recent 2014 service center dataset (31 cases) where WES was used more akin to a first line test and where we did not report incidental findings we identified:
  - Pathogenic or likely pathogenic variant(s) in 61.29% of cases
  - VUSs in 8 cases (not all will be pathogenic); 70% return?
What has been the impact?

• Where the sequencing was ordered from within our own Genomic Medicine clinics we can determine that the findings:
  – Modified care in 1/3 of cases
  – Selection of drugs or other therapies
Complex phenotypes can be caused by complex genotypes

- We and others are finding that ~1-2% of our patients have pathogenic variants with notable effect in two genes
  - Likely to be an over estimate because we are currently focused on cases with the most unusual phenotypes

- Even at 0.1% we would expect ~125,000 of the patients seen in US Genetics Clinics to fall into this category

- Without genome wide sequencing the clinical team would stop with the first positive single gene or other test

- This is likely to leave patients with a non-optimal treatment plan and less satisfactory outcome
Thanks!

• Families and Patients
• Referring Physicians
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Thanks!