RARE Webinar: Precision Medicine

Thursday, June 11, 2019
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Disclosures

Dawn Jacob Laney, MS, CGC, CCRC has disclosed that she has received honoraria and research funding as an investigator, researcher, speaker, board member registries/coordinator for Sanofi Genzyme; has received research funding and honoraria as an investigator, speaker, coordinator for Amicus and Shire, now part of Takeda; and is a co-founder and has stock options for ThinkGenetic, Inc.
Agenda

• Define precision medicine
• Discuss the goal of precision medicine in rare disease
• Review the role of genetics in precision medicine
• Barriers to precision medicine in rare disease
• Successes of precision medicine in rare disease
Precision Medicine

Identifying which treatment and dose will be most effective to treat a medical issue based on genetic, environmental, metabolic, and lifestyle factors.

https://visual.ly/community/infographic/health/we-are-all-zebras-how-rare-disease-shaping-future-healthcare
Precision vs. Personalized Medicine


National Cancer Institute: www.cancer.gov

Precision Medicine: The Goal

- Genetics (Genome)
- Patient Grouping
- Clinical trials
- Disease (Patient Doctor)
- Environment/Lifestyle
- Medication (Data)

RIGHT DRUG
RIGHT DOSE
RIGHT TIME
Genetics and Precision Medicine

https://www.undiagnosed.org.uk/support_information/what-is-exome-and-genome-sequencing/

https://www.my46.org/intro/whole-genome-and-exome-sequencing
Interpretation: Where The Rubber Hits The Road

- Did the doctor sending it in provide enough information about signs and symptoms?
- Do other relatives with the same variant have the same symptoms?
- Is a change already associated with health issues or treatment response?
- What research is available about this change and its impact on disease or treatment?
- What has changed in our genomic understanding since the LAST interpretation of these genetic findings?
Road Map: Precision Medicine in Rare Disease

1. Doctor reviews diagnosis and clinical history.
2. Determine if any genetic data supports a specific monitoring or treatment group.
3. Orders and/or reviews Genetic/Genomic testing.
5. Monitor treatment effectiveness and revise plan as needed.

GlobalGenes.org | #CareAboutRare
HELPING Precision Medicine in Rare Diseases

- Active patient support and advocacy groups
- Collaboration between patients, health professionals, researching, and pharmaceuticals.
- Rare disease registries providing additional information
- Seeking other genomic changes that impact outcomes and treatment
- Already precedent of FDA approval of specific treatment options within a subgroup of a rare disease population
Barriers To Precision Medicine In Rare Disease

- Access to testing: genomes and exomes are expensive and insurance often doesn’t cover them
- Not enough data about genetic variation and impact in treatment of rare diseases
- Some subgroups are so small it is hard to have clinical trials with enough power to be statistically significant
- It may be difficult to interest pharmaceuticals in developing a medication for a tiny subset of a rare disease
For Precision Medicine To Succeed Everyone Needs To Participate

• All of Us program
• Condition specific registries
• Participation in genomic/genetic substudies for therapy trials
• Patient advocacy involvement in designing studies and FDA process
Don’t Believe ALL the Hype

http://thedayexplorer.co.uk/

https://moneyweek.com/486743/genome-the-pharmas-making-pills-tailored-to-your-genes/
RARE Disease SUCCESS STORIES
Questions?

Contact Information:
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My Family Tree
Fabry Disease

Robert Hopkin
Cincinnati Children’s Hospital
Medical Center

Rob.Hopkin@cchmc.org
Presentation

• New born female with prenatal onset severe hydrocephaly
• Also has trachea-esophageal fistula and laryngeal cleft type 3, vascular ring with compression of the trachea, Fusion of ribs 8-9, and 14 pairs of ribs

• Initial evaluation failed to reveal a cause for the malformations
• She required multiple surgeries for examples:
  • Shunt placement
  • TEF and laryngeal cleft repair
  • G-tube placement
  • Repair of vascular ring
Presentation

• Developed multiple additional problems
  • Neurogenic bladder
  • Chronic pancreatitis
  • Developmental disability
  • Vocal cord paralysis
  • Post Traumatic stress
  • Chronic headaches
Genetic testing

- Chromosomes normal
- SNP microarray – Loss of heterozygosity on chromosome 3 (nonspecific abnormality that may or may not be associated with any problems)

- She is 19 years old and still without a diagnosis. She has a boyfriend. She and her parents are worried about her future and risks for any children she may have.
What do we know?
What do we need to know?
Is there a reason to do additional testing?
Test options

• Single gene disorders
  • Need to have a solid idea what you are looking for and only a few possible genes to consider

• Panel that is focused on particular problems
  • More genes but in this case you have brain malformation, heart malformation, laryngotracheal malformation, which do you choose?

• Whole exome or whole genome sequence
  • Just look at everything
  • Looking for any of literally billions of possible changes and there is a lot of normal variability
Whole Exome results

• RESULTS SUMMARY: Uncertain
• 1. Probable Disease Causing Variants or Variants of Unknown Significance Related to the Patient's Phenotype:
  • No variants were found in this category.
• 2. Additional Variants of Interest:
  • Heterozygous for c.1748G>A (p.Ser583Asn) in CHD7
• 3. Additional Medically Actionable Findings:
  • Heterozygous for c.1087C>T (p.Arg363Cys) in GLA
Who understands this and knows exactly what to tell the family?
Key points

• No diagnosis for the birth defects was found.

• The CHD7 mutation is shared with the mother
  • It should be autosomal dominant so the fact that her mother doesn’t have any disease is very important
  • This is likely to be a benign variant

• The GLA mutation is from her father
  • This is on the X-chromosome, so the father is at higher risk than his daughter.
  • This variant has been associated with a relatively late onset condition called Fabry disease. In adult men that can lead to heart disease, stroke, and / or kidney failure.
  • The risk is higher for men than women, but both can be affected.
So, now what?

• What does this mean for our patient?

• Is it important for her father?
Fabry disease

• Comes in 2 categories
  • Classical early on set disease usually severe untreated has life expectancy around 50 years and first symptoms in childhood
  • Non-classical highly variable symptom onset from early adulthood to 80s
    • Often only one body system with obvious problems, most frequently heart disease
Resolution

- The father is at highest risk for progressive heart disease with NONCLASSICAL Fabry disease
  - His mutation is predicted to respond to a newly approved oral chaperone therapy, but it has only been available for about a year. The standard option of IV infusion of the missing enzyme every 2 weeks could also be used.
  - He opted to be treated with the oral medication to prevent future heart or kidney disease.

- The daughter has many health problems but no abnormality typically seen in Fabry disease.
  - With the mutation she has many women will never become ill.
  - Those who have symptoms may develop heart disease in the 6th or 7th decade of life.
  - She opted for monitoring over time with no immediate intervention, but will need to have annual check ups and a heart evaluation every couple of few years. (she already needed that for her heart defect.)
Take home points

• We have many new powerful methods for making diagnosis of genetic disease
• Even the best most powerful tools we have are not completely successful (we currently can’t resolve about 30%)
• We may find unexpected risks that have important medical implications
• Families can manage this uncertainty well if we can help them understand it
Take home points

• By considering the details of findings in the context of the patient’s life we can modify treatment decisions even for rare disease
• Different management decisions may be used even for the same diagnosis
• Sometimes you need to consult with experts especially for rare or very rare conditions.
Acute Myeloid Leukemia with *FLT3* Mutation

Torsten Haferlach
MLL Munich Leukemia Laboratory
Case Report

• 62 year old man visited GP with fatigue and fever
• Blood counts:
  • Leukocytes 50 G/L (normal 4-10 G/L)
  • Hemoglobin 9 g/dl (normal 12-16 g/dl)
  • Platelets 80 G/L (normal 150 – 350 G/L)
• Transfer to hematologist, initiated in detail analyses of peripheral blood and bone marrow aspirate and biopsy
• Diagnosis: Acute Myeloid Leukemia (AML) with normal karyotype (46, XY) and with FLT3-ITD mutation, NPM1 not mutated
• 3 days later: patient sent to specialized clinic for start of treatment; Goal: CURE!
### Table 1. (continued)  
Acute myeloid leukemia (AML) and related neoplasms

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Cytogenetic Abnormalities</th>
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<tbody>
<tr>
<td>AML with recurrent genetic abnormalities</td>
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<tr>
<td>AML with t(8;21)(q22;q22.1); RUNX1-RUNXI1</td>
<td></td>
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<tr>
<td>AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBF-B-MYH11</td>
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<tr>
<td>APL with <strong>PML-RARA</strong></td>
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<tr>
<td>AML with t(9;11)(p21.3;q23.3); MLL3-KMT2A</td>
<td></td>
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<tr>
<td>AML with t(6;9)(p23;q34.1); DEK-NUP214</td>
<td></td>
</tr>
<tr>
<td>AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2; MECOM</td>
<td></td>
</tr>
<tr>
<td>AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1</td>
<td>Provisional entity: AML with BCR-ABL1</td>
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<tr>
<td>AML with mutated NPM1</td>
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<tr>
<td>AML with biallelic mutations of CEBPA</td>
<td>Provisional entity: AML with mutated RUNX1</td>
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<tr>
<td>AML with myelodysplasia-related changes</td>
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<tr>
<td>Therapy-related myeloid neoplasms</td>
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<tr>
<td>AML, NOS</td>
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<tr>
<td>AML with minimal differentiation</td>
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<tr>
<td>AML without maturation</td>
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<tr>
<td>AML with maturation</td>
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<tr>
<td>Acute myelomonocytic leukemia</td>
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<tr>
<td>Acute monocytic/monozytic leukemia</td>
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<tr>
<td>Pure erythroid leukemia</td>
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<tr>
<td>Acute megakaryoblastic leukemia</td>
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<tr>
<td>Acute basophilic leukemia</td>
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<tr>
<td>Acute panmyelosis with myelofibrosis</td>
<td></td>
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<tr>
<td>Myeloid sarcoma</td>
<td></td>
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<tr>
<td>Myeloid proliferations related to Down syndrome</td>
<td></td>
</tr>
<tr>
<td>Transient abnormal myelopoiesis (TAM)</td>
<td></td>
</tr>
<tr>
<td>Myeloid leukemia associated with Down syndrome</td>
<td></td>
</tr>
</tbody>
</table>

### Table 18. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex karyotype (3 or more abnormalities)</td>
</tr>
<tr>
<td><strong>Unbalanced abnormalities</strong></td>
</tr>
<tr>
<td>−7/del(7q)</td>
</tr>
<tr>
<td>del(5q)/t(5q)</td>
</tr>
<tr>
<td>i(17q)/t(17p)</td>
</tr>
<tr>
<td>−13/del(13q)</td>
</tr>
<tr>
<td>del(11q)</td>
</tr>
<tr>
<td>del(12p)/t(12p)</td>
</tr>
<tr>
<td>idic(X)(q13)</td>
</tr>
<tr>
<td><strong>Balanced abnormalities</strong></td>
</tr>
<tr>
<td>t(11;16)(q23.3;p13.3)</td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
</tr>
<tr>
<td>t(2;11)(p21;q23.3)</td>
</tr>
<tr>
<td>t(5;12)(q32;p13.2)</td>
</tr>
<tr>
<td>t(5;7)(q32;q11.2)</td>
</tr>
<tr>
<td>t(5;17)(q32;p13.2)</td>
</tr>
<tr>
<td>t(5;10)(q32;q21.2)</td>
</tr>
<tr>
<td>t(3;5)(q25.3;q35.1)</td>
</tr>
</tbody>
</table>

D. A. Arber et al., Blood, 127, 2391-2405, 2016
### Table 5. 2017 ELN risk stratification by genetics

<table>
<thead>
<tr>
<th>Risk category*</th>
<th>Genetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22.1); <em>RUNX1-RUNX1T1</em>&lt;br&gt;inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <em>CBFB-MYH11</em>&lt;br&gt;Mutated <em>NPM1</em> without <em>FLT3-ITD</em> or with <em>FLT3-ITD</em> low†&lt;br&gt;Biallelic mutated <em>CEBPA</em></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Mutated <em>NPM1</em> and <em>FLT3-ITD</em> high†&lt;br&gt;Wild-type <em>NPM1</em> without <em>FLT3-ITD</em> or with <em>FLT3-ITD</em> low† (without adverse-risk genetic lesions)&lt;br&gt;t(9;11)(p21.3;q23.3); <em>MLLT3-KMT2A</em>‡&lt;br&gt;Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>t(6;9)(p23;q34.1); <em>DEK-NUP214</em>&lt;br&gt;t(v;11q23.3); <em>KMT2A</em> rearranged&lt;br&gt;t(9;22)(q34.1;q11.2); <em>BCR-ABL1</em>&lt;br&gt;inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <em>GATA2,MECOM(EVI1)</em>−5 or del(5q); −7; −17/abn(17p)&lt;br&gt;Complex karyotype,§ monosomal karyotype&lt;br&gt;Wild-type <em>NPM1</em> and <em>FLT3-ITD</em> high†&lt;br&gt;Mutated <em>RUNX1</em>¶&lt;br&gt;Mutated <em>ASXL1</em>¶&lt;br&gt;Mutated <em>TP53</em>#</td>
</tr>
</tbody>
</table>

* *FLT3-ITD* low<br>Ratio <0.5<br>*FLT3-ITD* high<br>Ratio ≥0.5
Molecular markers = targets in AML

TCGA, NEJM, 368, 2059-2074, 2013
**FLT3 - Inhibitors**

P. P. Zarrinkar et al., Blood, 114, 2984-2992, 2009
AML tested for **FLT3-ITD + NPM1** (n=3.941; Age median = 68.4 range 18 - 100)

- **FLT3-ITD+ & NPM1+**
  - n=397 (10%)
- **FLT3-ITD+ & NPM1-**
  - n=320 (8%)
- **FLT3-ITD- & NPM1+**
  - n=592 (15%)
- **FLT3-ITD- & NPM1-**
  - n=2,632 (67%)
**FLT3-ITD in relapsed AML** (n=431; median = 63.5; range 19 - 85)

- **Primary diagnosis FLT3-ITD+**
  - n=161

- **Primary diagnosis FLT3-ITD-**
  - n=270

- **Relapse FLT3-ITD+**
  - n=124
  - **Relapse FLT3-ITD-**
    - n=37
  - **Relapse FLT3-ITD+**
    - n=35
  - **FLT3-ITD-**
    - n=235

**Status – Shift for FLT3-ITD: 17% of patients**

MLL Data August 2005 - September 2018
FLT3-TKD in relapsed AML (n=320; median = 63.1; range 19 - 85)

Primary diagnosis FLT3-TKD+ n=30

Relapse FLT3-TKD+ n=7

Relapse FLT3-TKD- n=23

Primary diagnosis FLT3-TKD- n=290

Relapse FLT3-TKD+ n=8

FLT3-TKD- n=282
<table>
<thead>
<tr>
<th>Treatment Strategies</th>
<th>Treatment Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML ≥60 y (See NCCN Guidelines for Older Adult Oncology)</td>
<td>Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on days 1, 4, and 7 (CD3-positive)³⁰</td>
</tr>
<tr>
<td>Intermediate-risk cytogenetics</td>
<td>Standard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) withidarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days ormitoxantrone 12 mg/m² x 3 days</td>
</tr>
<tr>
<td>Intermediate-risk cytogenetics and FLT3 mutant</td>
<td>Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and oral midostaurin 50 mg every 12 hours, days 8–21⁴⁴,⁴⁵</td>
</tr>
<tr>
<td>Therapy-related AML, Antecedent MDS/CML, Cytogenetic changes consistent with MDS (AML-MRC)</td>
<td>Dual-drug liposomal encapsulation of daunorubicin 44 mg/m² and cytarabine 100 mg/m² IV over 90 min on days 1, 3, and 5 x 1 cycle (category 1) orStandard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) withidarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days ormitoxantrone 12 mg/m² x 3 days</td>
</tr>
<tr>
<td>Unfavorable-risk cytogenetics (exclusive of AML-MRC)</td>
<td>Venetoclax once a day (100 mg d1, 200 mg d2, 400 mg d3 and beyond) and intravenous decitabine 20 mg/m² [days 1-5 of each 28-day cycle]⁵⁵,⁶⁶,⁶⁷ orVenetoclax once a day (100 mg d1, 200 mg d2, 400 mg d3 and beyond) and subcutaneous or intravenous azacitidine 75 mg/m² [days 1-7 of each 28-day cycle]⁵⁵,⁶⁶,⁶⁷ orVenetoclax once a day (100 mg d1, 200 mg d2, 400 mg d3 and 600 mg d4 and beyond) and subcutaneous low-dose cytarabine 20 mg/m²/day [days 1-10 of each 28-day cycle]⁵⁵,⁶⁶,⁶⁷ orLow-intensity therapy (azacitidine, decitabine)⁶⁶,⁶⁷ orStandard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) withidarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days ormitoxantrone 12 mg/m² x 3 days</td>
</tr>
<tr>
<td>Other recommended regimens for intermediate- or poor-risk disease</td>
<td>Standard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) withidarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days ormitoxantrone 12 mg/m² x 3 days</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of FLT3 inhibitors currently in clinical development.

<table>
<thead>
<tr>
<th>FLT3 inhibitor</th>
<th>Non-FLT3 targets</th>
<th>FLT3-TKD mutation activity</th>
<th>Single-agent CRc rates in R/R FLT3-mutated AML</th>
<th>Dose</th>
<th>Major toxicities</th>
<th>Approval status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>c-KIT, PDGFR, RAF, VEGFR</td>
<td>No</td>
<td>&lt;10%</td>
<td>400 mg bid</td>
<td>Rash, hemorrhage, myelosuppression</td>
<td>Available off-label [US FDA approved for hepatocellular, renal cell, and differentiated thyroid cancer]</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>c-KIT, PKC, PDGFR, VEGFR</td>
<td>Yes</td>
<td>&lt;10%</td>
<td>50 mg bid</td>
<td>GI toxicity, myelosuppression</td>
<td>US FDA and EMA approved for adults with newly diagnosed FLT3-mutated AML in combination with intensive chemotherapy [improves overall survival versus chemotherapy alone]</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>c-KIT, PDGFR, RET</td>
<td>No</td>
<td>24–47%</td>
<td>30–60 mg daily</td>
<td>QTc prolongation, myelosuppression</td>
<td>US FDA approval sought for use in relapsed/refractory setting [improves overall survival versus chemotherapy]</td>
</tr>
<tr>
<td>Crenolanib</td>
<td>PDGFR</td>
<td>Yes</td>
<td>17–39%</td>
<td>100 mg tid</td>
<td>GI toxicity</td>
<td>Drug development plan is focused on chemotherapy-based combination</td>
</tr>
<tr>
<td>Gilteritinib</td>
<td>AXL</td>
<td>Yes</td>
<td>37–41%</td>
<td>120 mg daily</td>
<td>Elevated transaminases, diarrhea</td>
<td>US FDA approved for adults with relapsed/refractory FLT3-mutated AML [full data not yet released]</td>
</tr>
</tbody>
</table>
Conclusions

- Diagnosis of leukemia needs cytogenetics and molecular genetics.
- Targeted treatment is possible.
- Transplant strategies follow biology of AML at diagnosis and treatment response (MRD).
- At relapse all diagnostic methods should be repeated.
- CURE is possible!
Submit Your Questions

To send in questions, please use WebEx’s Q&A feature in the bottom right hand corner
Thank You Panelists

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Torsten Haferlach
Prof. Dr. med, Dr. Phil
MLL Munich Leukemia Laboratory
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