JUST FOR YOU: GENOMIC TESTING AND PERSONALIZED CARE FOR RARE CANCERS

For sound, stream audio through your speakers. If you are having trouble accessing sound, please send a message using the chat box on the left hand side of the screen.

Alone we are rare. Together we are strong.
This webinar is being recorded.
Submit your questions using the chat function. It can be found at the left hand side of the window.
John Hopper
President of the Fibrolamellar Cancer Foundation
Co-Chair of NORD’s Rare Cancer Coalition

Jim Palma
Executive Director of the TargetCancer Foundation
Co-Chair of NORD’s Rare Cancer Coalition

Catherine Skefos, MA, MS, LGC
Genetic Counselor
Dana Farber

John Glod, M.D., PH.D.
Branch Clinical Director: Pediatric Oncology
NIH

Ellyn Goodrich
Cholangiocarcinoma Patient and Advocate
Rare Cancer Coalition – Objectives

• Form a close knit, multi-stakeholder community to work collaboratively on issues that the greater rare cancer community faces.

• While the patient organization coalition members are focused on different diseases, they face common challenges that may be more effectively addressed as a group.
It’s #RareCancerDay! Join Debbie Drell, NORD Membership Director as she shares facts about rare cancer from the NORD Rare Cancer Coalition!

Voices of Rare Cancer: Jeremy’s Story

In this week’s Voices of Rare Cancer feature, Jeremy shares his experience with pseudomyxoma peritonei (PMP), and the role genomic testing has played in his treatment.  ...Read more >
# Rare Cancer Coalition Activities

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 8-9</td>
<td>NORD Summit</td>
<td>Topics include patient-reported data and future of precision oncology!</td>
</tr>
<tr>
<td></td>
<td>Rare Cancer Track</td>
<td></td>
</tr>
<tr>
<td>Fall 2020</td>
<td>NORD Pod</td>
<td>Listen to our podcast on current events in rare cancer innovation</td>
</tr>
<tr>
<td></td>
<td>Rare Cancer Episode</td>
<td></td>
</tr>
<tr>
<td>Winter 2020</td>
<td>Rare Cancer Day Recap Webinar</td>
<td>For members of the RC Coalition</td>
</tr>
<tr>
<td>Feb 28, 2021</td>
<td>Rare Disease Day</td>
<td>Rare Cancer Coalition activities and presentations TBA</td>
</tr>
</tbody>
</table>

[Image: NORDpod logo]
Genomic Testing in Rare Cancers

John Glod, MD, PhD
Pediatric Oncology Branch
National Cancer Institute, National Institutes of Health
What is Genomic Testing?

DNA is isolated from a patient’s tumor sample.

Some DNA from some genes is sequenced.

The DNA sequence from the tumor is compared to normal DNA sequence.
Why do Genomic Testing?

• Diagnosis
• There are some mutations seen in tumors that suggest a specific treatment may work (example: NTRK gene fusions).
• Some mutations may indicate the a tumor is resistant to a particular drug.
• There are some instances when a DNA mutation in a tumor may suggest that there is a germline (heritable) mutation.
What do you do with the information in a genomic testing report?

Sometimes not enough DNA can be isolated to do sequencing.

A sample has both tumor cells and normal cells.

There are many mutations that we don’t understand how to interpret.

To really understand how a particular mutation impacts the efficacy of treatment it needs to be tested in a clinical trial. This can be challenging for Patients with rare tumors.
What do you do with the information in a genomic testing report?

### ADDITIONAL BIOMARKER FINDINGS

**Tumor Mutational Burden (TMB):** 0.786 Mutations/Megabase  
**Microsatellite Status (MS):** Stable

### 2. VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENOMIC LOCATION</th>
<th>TRANSCRIPT</th>
<th>NUCLEOTIDE CHANGE</th>
<th>AMINO ACID CHANGE</th>
<th>VAF* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAXX</td>
<td>chr6:33288963</td>
<td>NM_001350.4</td>
<td>c.689G&gt;T</td>
<td>p.Arg230Glu</td>
<td>63.80% (of 1267 reads)</td>
</tr>
<tr>
<td>FLI1</td>
<td>chr13:28919607</td>
<td>NM_002019.4</td>
<td>c.2310C&gt;T</td>
<td>p.Thr773Ile</td>
<td>27.00% (of 550 reads)</td>
</tr>
<tr>
<td>GRN2A</td>
<td>chr16:9858502</td>
<td>NM_000833.4</td>
<td>c.289G&gt;C</td>
<td>p.Val96Ile</td>
<td>52.00% (of 1599 reads)</td>
</tr>
<tr>
<td>LRP1B</td>
<td>chr2:141457963</td>
<td>NM_018557.2</td>
<td>c.665C&gt;T</td>
<td>p.Asp221Val</td>
<td>92.00% (of 857 reads)</td>
</tr>
<tr>
<td>MDC1</td>
<td>chr1:30672941</td>
<td>NM_014641.3</td>
<td>c.401A&gt;G</td>
<td>p.Ser134Arg</td>
<td>14.00% (of 685 reads)</td>
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<tr>
<td>NEGR1</td>
<td>chr1:77148984</td>
<td>NM_173888.3</td>
<td>c.54C&gt;G</td>
<td>p.Leu18Val</td>
<td>11.00% (of 782 reads)</td>
</tr>
<tr>
<td>SDHA</td>
<td>chr5:236556</td>
<td>NM_004166.4</td>
<td>c.1274T&gt;G</td>
<td>p.Val425Gly</td>
<td>5.15% (of 447 reads)</td>
</tr>
</tbody>
</table>

*VAF: Variant Allele Frequency

### 3. VARIANT INTERPRETATION

**Result:** 1 relevant variant was detected in this study.

**SUMMARY:**  
- The presence of a pathogenic variant in RET is consistent with the diagnosis of a phaeochromocytoma.  
- The T50500 Panel does not discriminate between germ-line and somatic events. Further studies are recommended to evaluate for MEN1.  
- An additional seven Variants of Unknown Clinical Significance were identified.

**Tier ZC: Pathogenic**  
- **RET** p.Met918Thr

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[rarediseases.org](http://rarediseases.org)
Genetic Counseling for Rare Cancers

Catherine Skefos MA, MS, CGC

Genetic Counselor
Dana Farber Cancer Institute
All cancer is genetic, but most is not hereditary.

- Environmental factors
- Lifestyle factors
- Aging process

- Sporadic
- Hereditary (~5-10%)
- Familial

(NORD - National Organization for Rare Disorders)

rarediseases.org
Somatic vs. Germline Testing

• Was this person *born with* a genetic mutation, or did they *acquire* it over their lifetime?
• Somatic testing done on tumor tissue
• Germline testing done on healthy tissue (blood, saliva, skin biopsy)
• If germline—
  • Implications for future cancer risk
  • Implications for family members
What is Genetic Counseling?

“The process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease” (NSGC)

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.
How do patients get referred to genetics?

• Cancer diagnosis
  • Certain cancers are more likely than others to have a hereditary component
    • Examples: ovarian cancer, pancreatic cancer, adrenocortical carcinoma, medullary thyroid cancer
  • Rare presentations of common cancers
    • Examples: breast cancer diagnosed <45 years old or in a male, metastatic prostate cancer, melanoma of the eye

• Family history
  • Multiple generations, younger ages of diagnosis, related cancer types, multiple primary cancers in one person

• Tumor testing results

A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
Tumor Testing ➔ Germline Testing
Why do we need both?

• Technologies differ between tests and institutions
• A germline mutation may be missed on somatic genomic testing depending on the type of testing done
• Referrals to genetic counseling should be made based on diagnosis or family history even when somatic genomic testing is uninformative
A small percentage of cancers (5-10%+) have an underlying hereditary cause.

Genomic testing of a tumor can lead to a referral to genetic counseling.

The genetic counseling process helps patients understand and make decisions about germline genetic testing.

Results of genetic testing can have impacts on the whole family.
Patient Story

Ellyn Goodrich
*Patient & Advocate*
**Patient Name:** Goodrich, Elynn  
**Report Date:** 29 March 2018  
**Tumor Type:** Liver cholangiocarcinoma

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Sex</th>
<th>Medical Facility</th>
<th>Ordering Physician</th>
<th>Additional Recipient</th>
<th>Medical Facility ID #</th>
<th>Pathologist</th>
<th>Specimen ID</th>
<th>Seattle Cancer Care Alliance - Eastlake</th>
<th>William Harris</th>
<th>Specimen Received</th>
<th>Specimen Site</th>
<th>Date of Collection</th>
<th>Specimen Type</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Medical Facility</td>
<td>ordering Physician</td>
<td>Additional Recipient</td>
<td>Medical Facility ID #</td>
<td>Pathologist</td>
<td>Specimen ID</td>
<td>Seattle Cancer Care Alliance - Eastlake</td>
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<td>Specimen Type</td>
<td>Black</td>
</tr>
</tbody>
</table>

**ABOUT THE TEST:**  
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

**PATIENT RESULTS**

- 5 genomic findings
- 2 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 6 clinical trials

**TUMOR TYPE: LIVER CHOLANGIOCARCINOMA**

Genomic Alterations Identified:

- **FGFR2** rearrangement intron 17
- **BAPI** G426R*S
- **CDKN2A** p.53INK4a W110* – subclonal

Additional Findings:

- Microsatellite status: MS-Stable
- Tumor Mutation Burden: TM-B-Low; 1 Muts/Mb

**For a complete list of the genes assayed and performance specifications, please refer to the Appendix.**

**THERAPEUTIC IMPLICATIONS**

<table>
<thead>
<tr>
<th>Genomic Findings</th>
<th>FDA-Approved Therapies (in patient’s tumor type)</th>
<th>FDA-Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2 rearrangement intron 17</td>
<td>None</td>
<td>Pazopanib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>BAPI</strong> G426R*S</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>CDKN2A</strong> p.53INK4a W110* – subclonal</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Microsatellite status</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Tumor Mutation Burden</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Note: Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have little or no evidence in the patient’s tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient’s tumor type.

For more comprehensive information please log on to the Interactive Cancer Explorer™  
To set up your interactive Cancer Explorer account, contact your sales representative or call 1-888-988-3639.
THIS AMENDED REPORT IS BEING ISSUED TO ADD GERMLINE AND RNA FUSION SEQUENCING RESULTS AND CORRECT SOMATIC VARIANTS BASED ON TUMOR/NORMAL PAIRED ANALYSIS.

The non-specific chromosomal rearrangement in FGFR2 was amended to reflect the presence of the FGFR2-VCL chromosomal rearrangement.

### GENOMIC VARIANTS

<table>
<thead>
<tr>
<th>Somatic - Potentially Actionable</th>
<th>Variant Allele Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1 p.G422fs Frameshift - LOF</td>
<td>30.7%</td>
</tr>
<tr>
<td>MTOR p.L2427Q Missense variant - GOF</td>
<td>27.2%</td>
</tr>
<tr>
<td>NRAS p.Q61K Missense variant (exon 3) - GOF</td>
<td>20.4%</td>
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<tr>
<td>FGFR2 - VCL Chromosomal rearrangement</td>
<td></td>
</tr>
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</table>

**Germline - Pathogenic / Likely Pathogenic**

No pathogenic variants were found in the limited set of genes on which we report.

### IMMUNOTHERAPY MARKERS

<table>
<thead>
<tr>
<th>Tumor Mutational Burden</th>
<th>Microsatellite Instability Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 m/MB</td>
<td>Stable</td>
</tr>
<tr>
<td>27th percentile</td>
<td>Equivocal</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

### FDA-APPROVED THERAPIES, OTHER INDICATIONS

<table>
<thead>
<tr>
<th>MEK Inhibitor</th>
<th>Binimetinib</th>
<th>NRAS p.Q61K Gain-of-function Clinical research, Melanoma: PMID 28284557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination (MEK Inhibitor + CDK4/6 Inhibitor)</td>
<td>Binimetinib + Ribociclib</td>
<td>NRAS p.Q61K Gain-of-function Clinical research, Melanoma: ASCO 2014 (abstr 9009)</td>
</tr>
<tr>
<td>mTOR Inhibitor</td>
<td>Everolimus</td>
<td>MTOR p.L2427Q Gain-of-function</td>
</tr>
</tbody>
</table>
FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion

On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib (PEMAZYRE, Incyte Corporation) for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

The FDA also approved the FoundationOne® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection.

Efficacy was investigated in FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least one prior therapy and had an FGFR2 gene fusion or rearrangement (clinical trial assay performed at a central laboratory). Patients received pemigatinib, 13.5 mg orally, once daily for 14 consecutive days, followed by 7 days off therapy.
For patients with cholangiocarcinoma, mutations matter.
Questions?

Submit your questions in the chat. Email additional questions to education@rarediseases.org

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