Implementing clinical whole exome sequencing for the care of children with Mendelian disorders and cancer

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Human Genome Sequencing Center
Baylor College of Medicine
Disclosures – Sharon E. Plon, MD, PhD

• I have the following financial relationships to disclose:
  – I am a member of the Baylor Genetics Scientific Advisory Board

• I will not discuss specific off label use and/or investigational use in my presentation.
DNA/WES Technology

Informatics

Process Management
Quality Control

Dept of Molecular and Human Genetics
Physicians/Counselors
Business Management
Sales/Marketing
Web Communications
Sales\Follow up
Regulatory
Clinical Exome Sequencing Timeline

2011
Clinical exome sequencing

2012
NHGRI CSER U01

2013
ACMG IF guidelines
NEJM 250 Cases

2014
JAMA 2000 and 800 cases; GIM 500 cases

2015
Exome related CPT codes
ACMG/AMP Variant Guidelines
Critical and prenatal exome

Original Article

Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D., Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S., Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D., Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D., Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D., Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D., James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D., Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.
Analysis of Next Gen Data for Clinical Reporting

Analysis focuses on genes with rare, protein-altering changes with appropriate mechanism of inheritance, in genes associated with disease.

- **Rare**: given the severity of the phenotypes, the allele should not be present at polymorphism frequency (1%) in control populations
- **Protein-altering**: most likely to have biological consequence (especially loss of function mutations)
- **Disease genes**: is this variant in a gene known to be associated with Mendelian disease (OMIM, Pubmed)
- **What is known about this particular variant (HGMD, ClinVar)**
- **ACMG/AMP Guideline for Variant Interpretation (Richards *GIM*, 2015)**

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Exome capture (VCRome 2.1) → Sequencing (Illumina HiSeq PE) → Genotyping (Atlas2 SNP/Indel) → Annotation (Type of Variant; Known Disease Allele) → Potential Disease Variant selection
Yang et al., JAMA, 2014 – Description of 2000 WES clinical cases

- 1780 predominantly pediatric patients (89%)
- 1440 (72%) have intellectual disability, seizure disorder or autism
- Diagnostic rate ~25% for patients referred for proband only WES.
- Now completed over 12,000 clinical cases
Mutations in Positive WES Cases

708 Mutant Alleles in the 504 Positives, 409 (58%) novel at time of reporting
Most Mutant Alleles Arose de novo
(AD: 74%; XL: 62%)
Multiple Mendelian Diagnoses in WES Cases

7374 sequential cases submitted for proband WES

• Diagnosis in 28.2% (2076/7374)
• Two or more diagnoses related to phenotype in 4.9% (101/2076) of diagnosed cases

Posey et al, *NEJM*, 2017
Rothmund-Thomson syndrome (RECQL4) and Xeroderma pigmentosum (XPC) share overlapping phenotypes such as skin and eyes. KBG syndrome (ANKRD11) and Ichthyosis vulgaris (FLG) exhibit distinct phenotypes like DD/DD, ID, seizures, facial, skeletal, skin, and cancer. The concept suggests that distinct phenotypes tend to have lower disease pair phenotype similarity compared to overlapping phenotypes. The hypothesis is supported by statistical analysis with p=5.1e-09 (Wilcoxon).
Diagnostic rate heavily dependent on newly discovered disease genes
WES re-analysis increases diagnostic rate over time

- Unsolved: 72%
- Solved in first analysis: 24%
- Solved in re-analysis: 4%

- New disease genes: 59%
- CNV analysis: 13%
- Parental analysis:
  - de novo: 12%
  - in trans: 6.8%
- Clinical update: 4.5%
- Coverage:
- Other

Pengfei Liu
Discovery of new disease genes is the greatest contributor to improved diagnostic rate

<table>
<thead>
<tr>
<th># of patients solved after re-analysis</th>
<th>Name of new disease genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5</td>
<td>DDX3X, PURA, TANGO2*, KAT6A, PIK3R1</td>
</tr>
<tr>
<td>3~5</td>
<td>SLC1A4, DNM1, POZ, AHDC1, ARID2, ECHS1, GNAO1, KCNA2, MAGEL2, SLC13A5, SOX5, WDR73</td>
</tr>
<tr>
<td>1~2</td>
<td>ASXL3, CHAMP1, CHD8, DEPDC5, HNRNPU, KCNT1, NALCN, PPP2R5D, PUF60, VARS2, WDR45, ADNP, CNTNAP1, DNMT1L, FBXL4, KCNC1, KMT2A, LAS1L, LIPT1, LZTR1, MED13L, MLL, NR2F1, PMPCA, RAB3GAP2, RARB, SERAC1, SSR4, STAMBPA, VRK1, ZBTB20</td>
</tr>
</tbody>
</table>
Use of Exome Sequencing for Infants in Intensive Care Units
Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management

Linyan Meng, PhD; Mohan Pamm, MD, PhD; Anirudh Saronwala, MD; Pilar Magoulas, MS; Andrew Ray Ghazi, BS; Francesco Vetrini, PhD; Jing Zhang, PhD; Weimin He, PhD; Avinash V. Dharmadhikari, PhD; Chunqing Qu, PhD; Patricia Ward, MS; Alicia Braxton, MS; Swetha Narayanan, MS; Xiaoyan Ge, PhD; Mari J. Tokita, MD; Teresa Santiago-Sim, PhD; Hongzheng Dai, PhD; Theodore Chiang, MSc; Hadley Smith, MPSA; Mahshid S. Azamian, MD, MPH; Laurie Robak, MD, PhD; Bret L. Bostwick, MD; Christian P. Schaaf, MD, PhD; Lorraine Potocki, MD; Fernando Scaglia, MD; Carlos A. Bacino, MD; Neil A. Hanchard, MD, PhD; Michael F. Wangler, MD; Daryl Scott, MD, PhD; Chester Brown, MD; Jianhong Hu, PhD; John W. Belmont, MD, PhD; Lindsay C. Bur sage, MD, PhD; Brett H. Graham, MD; Vernon Reid Sutton, MD; William J. Craig, MD, PhD; Sharon E. Plon, MD, PhD; James R. Lupski, MD, PhD, DSc(hon); Arthur L. Beaudet, MD; Richard A. Gibbs, PhD; Donna M. Muzny, MS; Marcus J. Miller, PhD; Xia Wang, PhD; Magalie S. Leduc, PhD; Rui Xiao, PhD; Pengfei Liu, PhD; Chad Shaw, PhD; Magdalena Walkiewicz, PhD; Weimin Bi, PhD; Fan Xia, PhD; Brendan Lee, MD, PhD; Christine M. Eng, MD; Yaping Yang, PhD; Seema R. Lalani, MD
Results of WES testing for 278 critically ill infants <100 days

- Overall 36.7% received a genetic diagnosis.
- Critical trio (14 day TAT) had a higher yield with 32 of 63 infants achieving diagnosis (50.8%).
- Diagnostic rate lower in children with cardiovascular disorders.
- Medical management was affected for 52.0% with diagnoses. These included:
  - Changing care or adding needed diagnostic testing.
  - Withdrawal of care in children with lethal diagnoses
Critical Trio Example

- Clinical presentation:
  - 4-day-old male
  - IUGR, admitted to NICU due to respiratory distress, pale skin, petechiae and bruising on chest and back
- Initial lab work revealed pancytopenia
- Critical trio WES (TAT 10d):
  - FANCA, c.154C>T (p.R52X), c.2852G>A, p.R951Q, both pathogenic, compound heterozygous
- Fanconi anemia, complementation group A [MIM: 227650]
Newborn diagnosis of Fanconi Anemia

• Represents an extraordinarily early presentation of FA
  – Average age of bone marrow failure – 6 years
  – Only a few other case reports of newborn presentation

• Clinical management after WES:
  – Postpone bone marrow biopsy
  – Early plan for bone marrow transplantation
  – Monitoring for other systems: renal ultrasound, echocardiogram
  – Early discharge and close follow up in clinic
Baylor College of Medicine BASIC3 Key Team Members

Sharon Plon
Murali Chintagumpala
Stacey Berg
Richard Gibbs
Christine Eng
David Wheeler

Sue Hilsenbeck
Laurence McCullough
Richard Street
Amy McGuire
Angshumoy Roy
Dolores Lopez-Terrada
**Study objectives:**

- To integrate information from **CLIA-certified germline and tumor exome sequencing** into the care of newly diagnosed solid and brain tumor patients at Texas Children’s Cancer Center.

- To perform parallel evaluation of the impact of tumor and germline exomes on families and physicians.
Original Investigation

Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors

D. Williams Parsons, MD, PhD; Angshumoy Roy, MD, PhD; Yaping Yang, PhD; Tao Wang, PhD;
Sarah Scollon, MS, CGC; Katie Bergstrom, MS, CGC; Robin A. Kerstein, BS, MT; Stephanie Gutierrez, BS;
Andrea K. Petersen, MD; Abhishek Bavel, MD; Frank Y. Lin, MD; Dolores H. López-Terrada, MD, PhD;
Federico A. Monzon, MD; M. John Hicks, MD, PhD, DDS; Karen W. Eldin, MD; Norma M. Quintanilla, MD;
Adekunle M. Adesina, MD, PhD; Carrie A. Mohila, MD, PhD; William Whitehead, MD; Andrew Jea, MD;
Sanjeev A. Vasudevan, MD; Jed G. Nuchtern, MD; Uma Ramamurthy, PhD; Amy L. McGuire, JD, PhD;
Susan G. Hilsenbeck, PhD; Jeffrey G. Reid, PhD; Donna M. Muzny, MSc; David A. Wheeler, PhD; Stacey L. Berg, MD;
Murali M. Chintagumpala, MD; Christine M. Eng, MD; Richard A. Gibbs, PhD; Sharon E. Plon, MD, PhD

JAMA Oncol. doi:10.1001/jamaoncol.2015.5699
Published online January 28, 2016.
### Race/Ethnicity of BASIC3 Subjects are Representative of Houston Population

Updated from Scollon et al., *Genome Medicine* 2014

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enrolled (n=239)</th>
<th>Declined (n=103)</th>
<th>P Value</th>
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<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>Hispanic</td>
<td>111 (46%)</td>
<td>41 (40%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>119 (50%)</td>
<td>52 (50%)</td>
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</tr>
<tr>
<td>Not reported</td>
<td>10 (4%)</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>White</td>
<td>141 (59%)</td>
<td>74 (72%)</td>
<td></td>
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<tr>
<td>Black or African American</td>
<td>25 (10%)</td>
<td>12 (12%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>10 (4%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>14 (6%)</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>42 (18%)</td>
<td></td>
<td></td>
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</tbody>
</table>
BASIC3 DIVERSE PEDIATRIC TUMOR DIAGNOSES

NON-CNS
- Neuroblastoma (19)
- Wilms tumor (15)
- Rhabdomyosarcoma (9)
- Germ cell tumors (15)
- Soft tissue sarcoma (7)
- Ewing’s sarcoma (6)
- Osteosarcoma (4)
- Hepatoblastoma (3)
- Mucoepidermoid carcinoma (3)
- Adrenocortical carcinoma (2)
- Hepatocellular carcinoma (2)
- Pheochromocytoma (2)

81/94 (86%)

CNS
- Medulloblastoma (11)
- Low grade glioma (11)
- High grade glioma (5)
- Glioneuronal tumors (5)
- Choroid plexus tumors (4)
- AT/RT (2)
- Meningioma (2)
- Pineoblastoma (2)
- Other (2)

40/56 (71%)

Tumor available for WES
Tumor WES Results (n=230)

HIGHEST category of mutation PER PATIENT

Categories of somatic mutations

I. Established clinical utility in tumor type
   - Example: ALK p.F1174L mutation (neuroblastoma)

II. Potential clinical utility
   - Example: KRAS p.Q61K mutation (neuroblastoma)

III. Consensus cancer genes
   - Example: PHF6 mutation (neuroblastoma)

IV. Other genes
   - Example: XIAP mutation (neuroblastoma)

Now converting to new AMP variant curation
Germline and/or somatic mutations with potential clinical relevance found in 40% of cases

Parsons et al., JAMA Oncology, 2016
Diversity of germline results returned

TUMOR REPORT

- All
- All Somatic
  - BRAF V600E

GERMLINE REPORT

- Cancer or Other Patient Phenotype
  - Pathogenic
  - VUS
  - Rare WT1 missense
  - DICER1 nonsense

- Other Medically Actionable
- PCG Genes
- Recessive Carrier Genes
  - Pathogenic
  - CFTR ΔF508

Gene Example

- FDA Indication
- CYP2A mut
- SCN5A mut

Opt-In

Scollon et al., Genome Medicine, 2014
Two Exome Reporting Teams Work in Parallel

Exome Sequencing with Pipeline Annotation

- Somatic Mutations
  - Molecular Pathology Review & Annotation
  - Tumor Exome Signout w/ Oncologists
    - Tumor Exome Report

- Germline Findings
  - Molecular Diagnostician review
    - Germline Exome Signout w/ Geneticists
    - Germline Exome Report
Variants of Uncertain “Clinical” Significance (VUS)

• Predominantly missense mutations in protein regions with or without known function.
• A variety of approaches including conservation, computational predictions, segregation with cancer and population studies are utilized to try and determine the significance.
• Different laboratories may report out same variant as a VUS or likely pathogenic or likely benign based on their laboratory’s criteria.
  – Data sharing through ClinVar and other databases helps to decrease discordance across laboratories.
Evaluation of *in silico* algorithms for use with ACMG/AMP clinical variant interpretation guidelines

Rajarshi Ghosh\(^1,2\), Ninad Oak\(^1,2\) and Sharon E. Plon\(^1,2\)*
Significant discordance of missense predications across algorithms in current use

Table 1 Concordance rate of different combination of algorithms

<table>
<thead>
<tr>
<th>Variant assertion in ClinVar</th>
<th>Variant source</th>
<th>Algorithms</th>
<th>Variants (n)</th>
<th>Concordance (n (%)</th>
<th>False concordance (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>ClinVar*</td>
<td>All 18</td>
<td>7346</td>
<td>382 (5.2)</td>
<td>57 (0.8)</td>
</tr>
<tr>
<td>Pathogenic</td>
<td>ClinVar*</td>
<td>All 18</td>
<td>7473</td>
<td>2930 (39.2)</td>
<td>2 (0.03)</td>
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<tr>
<td>Benign</td>
<td>ClinVar**</td>
<td>All 18</td>
<td>1914</td>
<td>86 (4.5)</td>
<td>12 (0.6)</td>
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<tr>
<td>Pathogenic</td>
<td>ClinVar**</td>
<td>All 18</td>
<td>1052</td>
<td>492 (46.8)</td>
<td>0 (0.0)</td>
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<tr>
<td>Benign</td>
<td>ClinVar*</td>
<td>Polyphen, SIFT, CADD, PROVEAN, MutationTaster</td>
<td>7346</td>
<td>2464 (33.5)</td>
<td>815 (11.1)</td>
</tr>
<tr>
<td>Pathogenic</td>
<td>ClinVar*</td>
<td>Polyphen, SIFT, CADD, PROVEAN, MutationTaster</td>
<td>7473</td>
<td>5904 (79.0)</td>
<td>68 (0.9)</td>
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<tr>
<td>Benign</td>
<td>ClinVar*</td>
<td>Polyphen, SIFT, CADD</td>
<td>7346</td>
<td>3392 (46.2)</td>
<td>1340 (18.2)</td>
</tr>
<tr>
<td>Pathogenic</td>
<td>ClinVar*</td>
<td>Polyphen, SIFT, CADD</td>
<td>7473</td>
<td>6342 (84.9)</td>
<td>156 (2.1)</td>
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</tbody>
</table>

ClinVar *: ClinVar variants with one star or above review status
ClinVar **: ClinVar variants with two stars or above review status
Assessment of algorithm performance across different disease mechanisms

VUS REPORTED in CANCER SUSCEPTIBILITY GENES (n = 215 germline exome reports)

median of 3 VUS (range from 0 to 10)
Evaluation of VUS reports in cancer susceptibility genes based on:
• Ethnicity (Hispanic vs non-Hispanic) – median = 3
• Race - increased VUS reported in African-Americans – median = 5

Hispanic: median = 3
Non-Hispanic: median = 3
African-American: median = 5
White: median = 3
Other: median = 3

p. = 0.65
p. = 0.0003
Cancer susceptibility molecular diagnosis in 9.8% (27/278) pediatric cancer patients

<table>
<thead>
<tr>
<th>Autosomal dominant (P/LP)</th>
<th>26</th>
<th>19 different genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes associated w/ specific childhood cancer</td>
<td>15</td>
<td>Examples include DICER1, VHLx3, MSH2, WT1x2, TP53x3</td>
</tr>
<tr>
<td>Genes not previously associated w/ specific childhood cancer</td>
<td>11</td>
<td>Examples include BRCA1x2, BRCA2, PALB2, CHEK2x2, FLCN, SMARCA4</td>
</tr>
</tbody>
</table>

| Autosomal recessive (biallelic) | 1 | TJP2 |

No one gene was reported in more than 3 BASIC3 patients: 3 each for VHL and TP53.
Germline results can have an impact on multiple family members

- 14 yo girl with glioblastoma
  - Mother aware of cancer family history but not in electronic medical record
  - Sequencing revealed \texttt{c.1697delA} frameshift mutation in \textit{MSH2} transmitted from her mother.

- \textit{MSH2} mutation associated with Lynch syndrome and glioma.
  - Cancer screening recommendations made for siblings, mother and other \textit{MSH2} positive family members
  - Now important for \textbf{treatment} decisions
Example of unexpected finding of mosaic WT1 mutation in patient with Wilms tumor

- **Subject 223202** – 9 mo male with Stage III Wilms tumor.
- No FH of cancer, no congenital anomalies and no genetic testing recommended.
  - WES revealed **mosaicism for frameshift in WT1**.
  - Complete loss of heterozygosity in tumor.
  - Finding of WT1 mutation resulted in long-term renal function assessment and more frequent contralateral kidney surveillance.

Angshumoy Roy
Newly described TSG with unexpected tumor: SMARCA4 LOF w/ neuroblastoma tumor
Can we predict which patients have findings?

<table>
<thead>
<tr>
<th>Column1</th>
<th>Cancer Diagnostic Finding</th>
<th>n=278</th>
<th>Yes (n=27) 9.8%</th>
<th>No (n=251)</th>
<th>p*</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>&lt;2</td>
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<td>43</td>
<td>6 (14%)</td>
<td>37 (86%)</td>
<td>0.6324</td>
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<td>2-12</td>
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<td>159</td>
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<td>145 (91.2%)</td>
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<td>&gt;12</td>
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<td>76</td>
<td>7 (9.2%)</td>
<td>69 (90.8%)</td>
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<td>135</td>
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<td>123 (91.1%)</td>
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<td>143</td>
<td>15 (10.5%)</td>
<td>128 (89.5%)</td>
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<td>121 (91%)</td>
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<td>14 (10.3%)</td>
<td>122 (89.7%)</td>
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<td>9</td>
<td>1</td>
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<td>Race</td>
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<td>0.6453</td>
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<tr>
<td>White</td>
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<td>159</td>
<td>13 (8.2%)</td>
<td>146 (91.8%)</td>
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<tr>
<td>Black</td>
<td></td>
<td>27</td>
<td>2 (7.4%)</td>
<td>25 (92.6%)</td>
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</tr>
<tr>
<td>other (American Indian, Asian, &gt;1 race)</td>
<td>37</td>
<td>1 (2.7%)</td>
<td>36 (97.3%)</td>
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<tr>
<td>NA</td>
<td></td>
<td>55</td>
<td>11</td>
<td>44</td>
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<tr>
<td>Tumor type</td>
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<tr>
<td>CNS</td>
<td></td>
<td>97</td>
<td>9 (9.3%)</td>
<td>88 (90.7%)</td>
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<tr>
<td>Non-CNS</td>
<td></td>
<td>181</td>
<td>18 (9.9%)</td>
<td>163 (90.1%)</td>
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* p-values were calculated by Fisher's exact test
Also little correlation with histologic diagnosis except rare tumors, e.g. PHEO, PPB

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>n=278</th>
<th>Yes (n=27)</th>
<th>No (n=251)</th>
<th>p*</th>
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<tr>
<td>ATRT</td>
<td>4</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
<td>0.337</td>
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<tr>
<td>CARCINOMA OTHER</td>
<td>14</td>
<td>3 (21.4%)</td>
<td>11 (78.6%)</td>
<td>0.144</td>
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<tr>
<td>CNS OTHER</td>
<td>20</td>
<td>1 (5%)</td>
<td>19 (95%)</td>
<td>0.704</td>
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<tr>
<td>EPENDYMOMA</td>
<td>11</td>
<td>0</td>
<td>11 (100%)</td>
<td>0.6081</td>
</tr>
<tr>
<td>EWING SARCOMA</td>
<td>13</td>
<td>1 (7.7%)</td>
<td>12 (92.3%)</td>
<td>1</td>
</tr>
<tr>
<td>GERM CELL TUMOR</td>
<td>24</td>
<td>0</td>
<td>24 (100%)</td>
<td>0.1449</td>
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<tr>
<td>HIGH GRADE GLIOMA</td>
<td>7</td>
<td>1 (14.3%)</td>
<td>6 (85.7%)</td>
<td>0.5149</td>
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<td>LIVER TUMOR</td>
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<td>2 (22.2%)</td>
<td>7 (77.8%)</td>
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<tr>
<td>LOW GRADE GLIOMA</td>
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<td>3 (9.7%)</td>
<td>28 (90.3%)</td>
<td>1</td>
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<td>MEDULLOBLASTOMA</td>
<td>18</td>
<td>1 (5.6%)</td>
<td>17 (94.4%)</td>
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<td>NEUROBLASTOMA</td>
<td>30</td>
<td>3 (10%)</td>
<td>27 (90%)</td>
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<td>NON-CNS OTHER</td>
<td>23</td>
<td>7 (30.4%)</td>
<td>16 (69.6%)</td>
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<td>0.3746</td>
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<td>19 (100%)</td>
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<td>WILMS TUMOR</td>
<td>26</td>
<td>3 (11.5%)</td>
<td>23 (88.5%)</td>
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<td>any SARCOMA</td>
<td>61</td>
<td>2 (3.3%)</td>
<td>59 (96.7%)</td>
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<td>SARCOMA w/out EWING</td>
<td>48</td>
<td>1 (2.1%)</td>
<td>47 (97.9%)</td>
<td>0.0587</td>
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Inheritance pattern of diagnostic mutations

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<td>Parental Samples Available</td>
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<td>Inherited from a parent</td>
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<tr>
<td>De novo (3) or mosaic (1)</td>
<td>4</td>
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<tr>
<td>Proportion inherited from a parent</td>
<td>80%</td>
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- 80% of alleles inherited!
- Equivalent maternal and paternal inheritance
- Parents have been very interested in having at-risk siblings tested for the mutations identified
Early Data on Clinical Utility: Cancer Surveillance
Recommendations for Germline Findings

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<td>Patient and sibling</td>
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<td>Parent only</td>
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<tr>
<td>Both</td>
<td>11</td>
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<tr>
<td>None</td>
<td>3</td>
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Examples of relevance

• Both parents & siblings: TP53, VHL
• Parents only: BRCA1, CHEK2
• No recommendations: KRAS, PTPN11, TJP2

• Cancer screening in siblings has been initiated through dedicated pediatric cancer screening clinic.
• Major focus of our CSER2 project.
Clinical Cancer Research is proud to present a special collection of articles from the AACR Childhood Cancer Predisposition Workshop. The initial series of manuscripts was generated by an international cohort of leading pediatric cancer experts in order to provide recommendations for screening surveillance of childhood cancer predisposition syndromes in an effort to facilitate early detection and treatment of pediatric cancers. We hope you enjoy this series of freely available articles and continue to check back for additional relevant content and updated recommendations.

- **The future of surveillance in the context of cancer predisposition: through the murky looking glass.**

- **Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr.**

- **Pediatric cancer predisposition imaging: focus on whole-body MRI.**
  Greer MLC…States LJ. Clinical Cancer Research June 2017.

- **Recommendations for surveillance for children with leukemia-predisposing conditions.**

- **Recommendations for childhood cancer screening and surveillance in DNA repair disorders**

- **Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood.**
Single pathogenic variants in genes for autosomal recessive cancer syndromes

- Total of 18/278 BASIC3 (6.5%) pediatric cancer patients had P/LP variants in a variety of recessive cancer syndrome gene.
- We subsequently reviewed medical findings at entry into study.
  - 0 of 18 subjects had clinical features of the recessive disorder except one patient with PFO and FANCL variant.
- Several of these reported variants were within Fanconi anemia genes (FANCC, FANCL, FANCM).
What is the expected frequency of Fanconi anemia pathway variants in pediatric patients undergoing WES?

• Evaluated the frequency of pathogenic or likely pathogenic (P/LP) variants in genes in the Fanconi pathway from Baylor clinical whole exome sequencing patients referred for non-cancer findings.

• We evaluated this frequency in each of 15 FA genes: FANCA, B, C, D1/BRCA2, D2, E, F, G, I, J/BRIP1, L, N/PALB2, O/RAD51C, P/SLX4 and BRCA1 (FA-like condition, FANCS)
Clinical BCM non-cancer WES Cohort (n= 9986)

- As previously reported (Yang et al., JAMA, 2014) patients referred for clinical WES are predominantly in pediatric age range: 88% <18 years
- Referred for WES from a wide variety of medical centers.
- Most common indications are neurologic, intellectual disability and/or congenital anomalies.
- Data provided here is variants detected in proband:
Frequency of 3 autosomal dominant cancer susceptibility genes: *BRCA1*, *BRCA2*, *PALB2*

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<th>Gene</th>
<th>Heterozygous Patients</th>
<th>Carrier frequency</th>
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<td>20</td>
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<td>BRCA2</td>
<td>31</td>
<td>0.31%</td>
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<tr>
<td>PALB2</td>
<td>10</td>
<td>0.10%</td>
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FA Carrier Status per Gene – summing across all FA gene = 2.92%
Nature of the pathogenic FA alleles found in non-cancer WES cohort

• 10% of BRCA1 and 5% of BRCA2 reported P/LP variants were missense alleles, whereas all other variants in FA genes were predicted to be truncating.

• Similarly, 90% of BRCA1 and 92% of BRCA2 mutations were previously reported in the literature where only 47% of the pathogenic variants in the other FA genes were previously reported.
Conclusions of Fanconi/BRCA Analysis

• Clinical WES of a large primarily pediatric cohort:
  – Approximately 2.9% are carriers of a Fanconi allele
  – This includes ~0.5% with either BRCA1 or BRCA2
• Now doing a comparison with Geisinger ~10K pediatric exomes to generalize the findings.
• This data provides framework for comparing findings in these genes in pediatric cancer cohorts, BASIC3, PCGP, TARGET, etc.
Clinical Expectations/Utility in BASIC3

• We prospectively evaluated whether standard clinical practice for genetic testing could predict the WES findings (or did the exome provide more information):
  – At entry, the BASIC3 clinical genetics team reviewed tumor pathology, family and medical history in the EMR and any study related surveys:
  – We determined if genetic testing would be considered for the patient based on clinical features?
  – If so, what genes or tests would be ordered?

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<th>#pts</th>
<th>Gene test considered</th>
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<td>No</td>
<td>176</td>
<td>microarray</td>
<td>19</td>
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</table>

Katie Bergstrom, CGC Sarah Scollon, CGC and Sharon Plon, FACMG
We found poor ability to predict which BASIC3 subjects would have molecular diagnosis

• Only 11 of 27 (41%) patients with diagnostic cancer susceptibility findings were predicted at entry.

• Variety of reasons subjects were missed:
  – Didn’t recommend testing for genes like BRCA1
  – Diagnoses that we might think are obvious (PTPN11/Noonan) were not considered by oncologists prior to the WES results.
  – Clinically, relevant molecular findings like de novo or mosaic WT1 mutations in unilateral Wilms patients.
Need to anticipate ongoing evolution of variant interpretation (first reports in 2012)

- Child with pleomorphic xanthoastrocytoma and delayed speech
- History of tumors in maternal & paternal lineage
- Germline WES – pathogenic variant in DKC1 - gene associated with dyskeratosis congenita
  - C.-142c>G in DKC1 shared by mother; reported in article in Human Genetics 2001 in patient with DKC and functional study showed that it disrupted sp1 binding site
- Referred to Alison Bertuch, who tested patient for peripheral blood telomere length, which was normal
- Now in gnomad database of 100K individuals
  - There are 16 hemizygotes (from ~50K males)
  - Unlikely this variant would be called pathogenic today
BASIC3 Conclusions and Recommendation

• Multiple studies demonstrate that ~10% of diverse pediatric cancer populations carry P/LP variants in wide range of dominant cancer susceptibility genes.
  – Mixture of genes with with and without prior association with the child’s tumor diagnosis
  – Another ~6% carry single recessive alleles (no clear clinical significance or evidence of enrichment over controls).

• Current clinical practice for genetic evaluation may miss >50% of these children including clinically relevant germline findings for patient families.

• Time to develop clinical guidelines with germline panel/WES for all childhood cancer patients.
Contrasting WES results in pediatric cancer and neurodevelopmental cohorts

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<th>Pediatric Cancer</th>
<th>Neurodevelopmental</th>
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<td>Diagnostic rate of ~10%</td>
<td>Diagnostic rate of 25%</td>
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<tr>
<td>Autosomal dominant disorders predominate</td>
<td>More equal mixture of AD, AR and XLR</td>
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<tr>
<td>Small numbers but ~80% inherited from parent</td>
<td>De novo mutations (~70%) predominate (multiple DNM)</td>
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<tr>
<td>Results frequently impact screening &amp; surveillance recommendations</td>
<td>Results used for diagnosis and refining recurrence risk for parents</td>
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<tr>
<td>Tumor data can be used to aid interpretation of germline genome</td>
<td>Relatively rapid identification of new germline disease genes</td>
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</table>
KidsCanSeq – Next phase of CSER project

Figure 1

Study sites

- TCH/BCM (Houston)
- VCCC: TCH Vannie Cook Cancer Clinic (McAllen)
- Cook: Cook Children’s (Fort Worth)
- CHOSA: Children’s Hospital of San Antonio
- UTHSC-SA: UT Health Science Center – San Antonio
Sequencing plan – direct comparisons of clinical utility with targeted panels

Figure 2

Newly diagnosed patients (n=250/yr)

Germline (blood) sequencing: all patients
(n=300/yr)

Tumor (FFPE) sequencing:
High risk & relapsed patients only
(n=100/yr)

Non-high risk
n=200/yr

High risk
n=50/yr

Relapsed
n=50/yr

Relapsed patients (n=50/yr)
A Clinical Sequencing Exploratory Research (CSER) project
Supported by NHGRI/NCI 1U01HG006485

BASIC³ Project 1 (clinical)
• Sharon Plon, MD, PhD (Project PI)
• Will Parsons, MD, PhD (Project PI)
• Murali Chintagumpala, MD (co-I)
• Stacey Berg, MD (co-I)
• Susan Hilsenbeck, PhD (co-I)
• Tao Wang, PhD (co-I)

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• Sarah Scollon, MS, CGC
• Katie Bergstrom, MS, CGC
• Stephanie Gutierrez (Data manager)
• Ryan Zabriskie (Laboratory manager)

TCH/BCM Pathology
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• Dolores López-Terrada, MD, PhD
• Adekunle Adesina, MD, PhD

TCH Surgery and Neurosurgery

BCM/TCH leadership
• David Poplack, MD
• Susan Blaney, MD
• Arthur Beaudet, MD
• James Versalovic, MD, PhD
• Jed Nuchtern, MD

BASIC³ Project 2 (sequencing and reporting)
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• Christine Eng, MD (co-PI)
• Yaping Yang, PhD (co-I)
• Angshumoy Roy, MD, PhD (co-I)
• David Wheeler, PhD (Co-I)
• Donna Muzny, MS

BASIC³ Project 3 (ELSI)
• Laurence McCullough, PhD (co-PI)
• Richard Street, Jr., PhD (co-PI)
• Amy McGuire, JD, PhD (co-I)
• Melody Slashinski, PhD (co-I)
**Objective:** to open a COG-wide single stage phase II trial of genomically-directed therapies for children with refractory solid tumors and lymphomas.
Primary objectives

• To determine the objective response rate in patients with *a priori* specified genomic alterations treated with pathway-targeting agents

• To determine the proportion of patients whose tumors have pathway alterations that can be targeted by existing drugs

• To demonstrate the feasibility of analyzing genetic pathway alterations in refractory/recurrent pediatric tumors in a timeframe that permits use of the results to guide therapy choices

• Germline analysis is not a primary objective
Study Overview

Children with relapsed and refractory solid tumors and lymphomas

APEC1621SC: Screening protocol

- Tumor biopsy
- Genetic sequencing
- Actionable mutation detected

Matching study agent selected

- SD, CR or PR
- Continue until progression
- PD

Available MATCH study agents

- Purple
- White
- Light blue
- Orange
- Red
- Black
- Yellow
- Green

Another actionable mutation detected?

- Yes
  - Off study
- No

APEC1621A-Z: Phase 2 treatment protocols

- N=20 per arm
- Small expansion cohorts
- 7 arms (agents) to start
- Non-histology driven
- Estimated 200-300 subjects/year

Modular format

Single stage phase II studies
Clinical Sequencing

- FFPE tumor samples
- Oncomine DNA/RNA mutation panel (Life Technologies/Thermo Fisher Scientific)
  - >140 genes
  - >4000 mutations of interest
  - defined set of SNVs, indels, CNVs, gene fusions
- Analytic pipeline adapted for pediatric study
- Sequencing to be performed at two existing NCI-MATCH laboratories
- Germline sequencing performed in parallel with results reported separately
Germline Reporting Committee Goals

• **Mission:** To devise and implement a procedure for the return of germline pathogenic cancer susceptibility mutation results (or other incidental findings) identified in study subjects.

• **Specific tasks:**
  – Develop a plan for the return of results obtained by clinical sequencing of study subjects
  – Develop a plan for the return of results (if indicated) from additional (non-clinical) research sequencing studies
## Genes for germline reporting – those with known cancer susceptibility phenotype

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<th>CNV</th>
<th>Hotspot</th>
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Summary of early MATCH germline results

• The steps needed to review and generate germline reports has been developed and put into place.
• Given recent studies we expect that most of the germline reports to be negative.
• Already have examples where germline reports (a) exclude possible diagnosis, (b) confirm known diagnosis or (c) provide unexpected cancer susceptibility information.
• Educational materials and website being developed.
• Genetics resource center to support oncologists receiving reports is available.
Project Updates - Enrollment

- 31 patients have been enrolled on the screening protocol (APEC1621SC) as of 10/31/17
- 18 patients have had tumor sequencing completed
- 5 patients have been matched to treatment protocols
- Already have examples where germline reports:
  (a) exclude possible diagnosis
  (b) confirm known diagnosis
  (c) provide unexpected cancer susceptibility information
NCI-COG Pediatric MATCH Study

Study committees
• Study design and logistics: Stacey Berg, Beth Fox
• Target/agent prioritization: Katie Janeway, Jae Cho
• Sequencing platform/analysis: Will Parsons, Jim Tricoli
• Germline result reporting: Sharon Plon, Steven Joffe
• Biospecimens: Julie Gastier-Foster
• Informatics: Hema Chaudhary, David Patton

COG leadership and staff
• Peter Adamson, Catalina Martinez, Rita Tawdros, Wendy Martinez, Todd Alonzo, Thalia Beeles, Heather Day…

NCI/CTEP leadership and staff
• Nita Seibel (NCI study PI), Malcolm Smith, adult NCI-MATCH leadership (Conley, Chen, Williams, Patton)…

FDA leadership
• Martha Donoghue, Greg Reaman
Questions?
Genetic knowledge and parental ethnicity

<table>
<thead>
<tr>
<th>Genetic knowledge</th>
<th>All subjects</th>
<th>Hispanic or Latino n=60</th>
<th>Non-Hispanic n=80</th>
<th>Wilcoxon rank sum test P</th>
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<td>Range (4-10)</td>
<td>Range (6-10)</td>
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<td>Sum score</td>
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<td>9</td>
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Interaction between ethnicity, education, and genetic knowledge
Parents preferences for decision making role

Select the phrase that best describes the role you have actually taken with your child’s doctor in dealing with your child’s healthcare:

1. I prefer to make the final selection about which treatment my child will receive
2. I prefer to make the final selection of my child’s treatment after seriously considering my child’s doctor’s opinion
3. I prefer that my child’s doctor and I share responsibility for deciding which treatment is best for my child
4. I prefer that my child’s doctor makes the final decision about which treatment will be used, but seriously considers my opinion
5. I prefer to leave all decisions regarding my child’s treatment to my child’s doctor