Participants’ Questions and Comments when Learning their Children’s *CYP2D6* Research Results

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Plan

• Provide overview of larger study from which three abstracts emerged

• Present individual projects
  – Discuss parents' informational needs when returning children’s pharmacogenomic research results
Background

• Growing number of network RFAs contain expectation to study return of individual genomic research result
  – RFA-HG-10-009, The Electronic Medical Records and Genomics (eMERGE) Network, Phase II
    • RFA-HG-11-022 (Addition of Pediatric sites)
• Joint eMERGE application submitted by Cincinnati Children’s Hospital Medical Center (CCHMC) and Boston Children’s Hospital (BCH)
  – John B. Harley, MD, PhD (PI)
CCHMC/BCH eMERGE Return of Genomic Research Results

- **Aim:** Use return of CYP2D6 research results to explore parents’ response to and use of their children’s research results and better understand the factors that influence their decisions about learning incidental findings

- **Hypothesis:** There will be a difference in reported likelihood of parents’ sharing their child’s CYP2D6 pharmacogenetic result in the case and control groups
  - Cases: Parents of children previously exposed to opioid
  - Controls: Parents of children naïve to opioids
Why *CYP2D6*?

- IRBs reluctant to approve protocols with return of individual genomic research results in 2011
- *CYP2D6* genotyping provided in CCHMC clinical molecular genetics laboratory since 2004
- *CYP2D6* enzyme important for metabolism of many medications
- 5 – 10% population have 2 *CYP2D6* genes that do not make enzyme (poor metabolizers); 1 – 3% have 3 or more *CYP2D6* genes that make functional enzyme (ultra-rapid metabolizers)
Why CYP2D6?

- Differences in CYP2D6 enzyme may affect how a person responds to certain medicines
- Guidelines for codeine use based on CYP2D6 genotype ([https://www.pharmgkb.org/guideline/PA166104996](https://www.pharmgkb.org/guideline/PA166104996))
  - Avoid codeine in poor metabolizers (ineffective pain relief)
  - Avoid codeine in ultra rapid metabolizers (increased risk for serious side effects)
- Codeine commonly used for pain management in pediatric settings
Methods

• Recruited parents whose children had stored DNA for future research
• After enrollment, children’s stored DNA samples were assayed for 20 different forms of CYP2D6 and full gene duplication, gene deletion
• Result delivered by telephone to parent
• Call transferred for close ended survey
  – To learn responses to results (Carrie will describe)
• 60 invited to participate in interview
  – To more fully understand responses to results (Sarah will describe)
~3000 Invited

98 Cases, 105 Controls, = 203 Enrolled

74 Cases, 99 Controls = 173 Genotyped

Cases 57, Controls 71 = 128 Results Returned

30 Awaiting genotyping

6 failed genotypes
29 unable to reach
10 to be scheduled

4 turned 18 years before parent disclosure
1 parent not surveyed

Cases 55, Controls 68
123 Surveyed

Cases 30, Controls 31
61 Interviewed
Telephone Scripts for Result Disclosure

- Developed by CCHMC & BCH professionals to assure consistency in messaging
  - Pre-tested with study staff, family, friends with limited knowledge about genetics
  - Genotype and phenotype terminology removed, substituted with descriptive language
    - Number of CYP2D6 genes that make enzyme, make enzyme that may not work as well as expected, or do not make enzyme
  - Measured readability: 7th grade level
<table>
<thead>
<tr>
<th>Genotype Description</th>
<th>Meaning</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CYP2D6 gene that… makes normal amount of enzyme / may not work as well as expected</td>
<td>This means… less may be broken down to morphine. Less morphine means codeine may not work well to lower [child’s name] pain.</td>
<td>If [child’s name] is given codeine in the future and it doesn’t help to lower his/her pain, ask your doctor if a different pain medicine can be prescribed</td>
</tr>
<tr>
<td>- And -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CYP2D6 gene that… may not work as well as expected / does not make enzyme</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Potentially Actionable Category
• Inhibitors (some medicines can interfere with codeine…)
  – It is important to tell the doctor all the medicines and supplements [child’s name] is taking
• Risk for side effects not eliminated
  – You should call your doctor if a pain medicine causes [child’s name] to vomit, become confused, have breathing problems or sleep so deeply it is hard to wake [him/her] up
• Summary: The CYP2D6 result means….
Telephone Disclosure Process

• All results returned by 1 APRN with specialty education & training in genetics
• Call transferred to another study staff for survey
• Copy of script with parents’ questions, comments and APRN’s responses mailed to parent along with $10 gift card
Post Hoc Research Question

• What type of information do parents seek beyond that provided in the script?
  – Implications for knowledge needed by professional returning pharmacogenomic research result
  – Implications for resources needed when considering return of incidental or secondary genomic research results
Sub-Study Method

• Scripts were amended with parent questions, comments and APRN responses.
  – Documented for participants’ records
  – Analyzed for categories of participants’ information needs beyond baseline script content
• Atlas.Ti, v7.5.4 used for content analysis
## Participant Disclosure Demographics

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers / Fathers / 18 year olds</td>
<td>59 / 2 / 1</td>
<td>63 / 0 / 3</td>
<td>128</td>
</tr>
<tr>
<td>Age: Median (IQR)</td>
<td>40 (35-47)</td>
<td>46.5 (43-51)</td>
<td>45 (39-50)</td>
</tr>
<tr>
<td>Race: N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White / Caucasian</td>
<td>56 (90.3)</td>
<td>62 (93.9)</td>
<td>118 (92.2)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>4 (6.5)</td>
<td>3 (4.5)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.2)</td>
<td>1 (1.5)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Education: N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 12\textsuperscript{th} grade</td>
<td>9 (14.5)</td>
<td>12 (18.2)</td>
<td>21 (16.4)</td>
</tr>
<tr>
<td>≤ 4 years college</td>
<td>40 (64.5)</td>
<td>43 (65.2)</td>
<td>83 (64.8)</td>
</tr>
<tr>
<td>&gt; 4 years of college</td>
<td>12 (19.4)</td>
<td>11 (16.7)</td>
<td>23 (18.0)</td>
</tr>
</tbody>
</table>
## Discussion Categories Beyond Script

<table>
<thead>
<tr>
<th>Discussion Categories</th>
<th>Participants N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>59 (46.1)</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td>57 (44.5)</td>
</tr>
<tr>
<td>Genetics</td>
<td>31 (24.2)</td>
</tr>
<tr>
<td>No questions or discussion</td>
<td>48 (37.5)</td>
</tr>
</tbody>
</table>
Past experiences with pain medicine

Complex health care needs

Side effects

Past experiences with other medicines

Clinical discussions

Referral recommended

70 comments / questions

18 comments / questions

6 comments / questions

4 comments / questions

27 responses
Pharmacogenetic discussions

- Pain medicine options
  - CYP2D6 role in other medicines
    - Inhibitors
    - CYP2D6 other roles
- Addiction risk
- Cost of CYP2D6 test

Questions and responses:
- Pain medicine options: 37 questions / responses
- CYP2D6 role in other medicines: 36 questions / responses
- Inhibitors: 17 questions / responses
- CYP2D6 other roles: 12 questions / responses
- Addiction risk: 6 questions
- Cost of CYP2D6 test: 1 question
Past Experiences with Pain Medicines

• P7, Remarked she now understood her own past side effects from morphine
  – Clarify CYP2D6 enzyme breaks down codeine to morphine but does not break down morphine
    • CYP2D6 test does not help us understand morphine response
• P22, “This is making sense now. Vicodin makes me sick but doesn’t help my pain”
  – P7 & P22 Participants interpreting child’s result as explanation for their personal experiences
    • Clarify inheritance
    • Provide information about clinical laboratories (referral)
Pain Medicine Options

- P34 “Should the doctor increase her codeine dose?”
  - No. Codeine can cause side effects even if it isn’t broken down to morphine.
- P116: Commented that child had “Vicodin with codeine” to treat pain after a broken arm that required pins. He didn’t have anything serious happen… He just slept the whole day…
  - Clarify medication
  - Validate sleeping all day is side effect
  - Provide pain medicine options that do not need CYP2D6 enzyme…
Pharmacogenetics: Inhibitors

• P94, Commented child was taking Prozac
  – Recognize this is a CYP2D6 inhibitor
  – Explain potential impact on available CYP2D6 enzyme when taking codeine
  – Explain potential impact on codeine’s ability to lower pain
  – Discuss alternative pain medicine options
Discussion

- This study provides insight into the type of conversations parents and researchers might have regarding pharmacogenetic results.
- Incidental findings of variant genes associated with variability in medication response are not uncommon with whole genome sequencing (Dewey et al 2014; Weitzel et al 2014).
- Validated incidental genomic research results of an actionable medical nature should be offered to research participants (Jarvik et al 2014).
- Personal pharmacogenetic test results reported to be important by adult participants (Madadi et al 2010).
Implications

• Research teams need to identify available professional and/or education resources to address research participants’ information needs regarding pharmacogenetic results.

• Teams should anticipate comments and questions related to a research result’s relevance for current medicines as well as past experiences with other medicines and disease processes.
  – PharmGKB comprehensive resource
    • Clinical Pharmacogenetics Implementation Consortium (CPIC) produces and publishes peer reviewed guidelines
    • Access to drug labels with pharmacogenetics information
    • Drug pathways, drug response gene summaries, other information resources
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References


