Prior opioid exposure influences parents' sharing of their children's *CYP2D6* research results

Aim: To determine parents' use of their children's *CYP2D6* research result. We hypothesized that perceived utility, likelihood of sharing and actual sharing of results would differ between parents with children previously exposed (cases) or unexposed (controls) to opioids. **Methods:** We returned results by phone (baseline). We surveyed parents about perceived utility and likelihood of sharing their child's research result at baseline, and actual sharing at 3 and 12 months. **Results:** Cases were more likely than controls to agree that they ($p = 0.022$) and the doctors ($p = 0.041$) could use the results to care for their child, to report higher likelihood of sharing ($p = 0.042$) and to actually share results with the child's doctor ($p = 0.026$). **Conclusion:** Prior opioid exposure influenced perceived clinical utility and sharing behaviors.

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Genomics research to advance the science of medicine and improve the effectiveness of healthcare is part of the National Human Genome Research Institute's research agenda and large research networks are beginning to explore how return of actionable genetic variants to patients and clinicians impacts clinical care and health outcomes [1]. Although the literature has concentrated on determining actionability of gene variants associated with disease or disease risk [2], pharmacogenetics incidental findings can also be identified through SNP chip and exome sequencing data [3] as well as through large gene panels [4]. Guidelines with therapeutic recommendations based on pharmacogenetics results exist [5], suggesting that pharmacogenetics findings may increasingly be considered returnable if identified in genomic research studies. There is clear evidence that the public [6–12], parents and pediatric and adult patients [13–17], and research participants [18,19] want the option

to learn actionable genomic research results. However, there are few reports of what participants actually do with the results [20]. The presence of *CYP2D6* guidelines for codeine, a medication relevant to children [21,22], provided an opportunity to study the return of a genetic research result that is potentially actionable during childhood.

Codeine as a combination product is categorized as a Schedule III controlled substance and until very recently [23] was one of the commonly prescribed opioids for pain management in children [24–26]. Variability in codeine's analgesic effectiveness and toxicity-related adverse drug reactions (ADRs) have been linked to variability in *CYP450 2D6* (*CYP2D6*) enzyme activity [27–29]. In April 2017, the US FDA issued a contraindication to using codeine and tramadol for pain management or codeine for cough in children under 12 years of age [23]. Yet, evidence-based guidelines are available for codeine administration or avoidance

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when *CYP2D6* gene results are known. The guidelines also include information about tramadol, oxycodone and hydrocodone [21,22].

Codeine is metabolized by *CYP2D6* enzyme to its analgesic metabolite, morphine. The *CYP2D6* gene is highly polymorphic and allele frequencies differ across populations [30]. Alleles are classified as leading to increased, normal, decreased or no *CYP2D6* enzyme function. A person's resulting *CYP2D6*-metabolizing capacity is predicted by diplotype to be ultrarapid, normal, intermediate or poor [30,31]. People who are ultrarapid metabolizers are expected to metabolize a greater proportion of codeine to morphine, increasing risk for serious ADRs [28]. People who are poor metabolizers are unable to convert codeine to morphine and are thus not expected to experience analgesia [27]. Tramadol, hydrocodone and oxycodone are also metabolized to more active analgesic metabolites by *CYP2D6* in varying degrees, but the evidence for therapeutic effects is not as clear as that for codeine.

There is little information regarding whether parents feel that pharmacogenetics research results are clinically useful and with whom parents intend to [32] and actually share their child's pharmacogenetics testing information. In addition, there is no information regarding how a child's past exposure to prescribed pain medication influences a parents intended and actual sharing of pharmacogenetics test results. We sought to determine whether perceived utility of *CYP2D6* research results differed between parents whose children had a history of exposure to a prescribed opioid (cases) and parents whose children had no history of exposure to a prescribed opioid (controls). We also sought to determine whether parents' reported likelihood of sharing, and actual sharing of their child's *CYP2D6* pharmacogenetics test result with their child's doctor, pharmacist and child differed between cases and controls. We hypothesized that there would be a difference between cases and controls in perceived utility, reported likelihood and actual sharing of their child's *CYP2D6* pharmacogenetics result.

Methods

Study population

English-speaking mothers or fathers whose children were previously enrolled in one of three institutional review board (IRB)-approved protocols in which stored DNA was available for future research were eligible to participate in the current study (Figure 1). These studies were: Personalizing Perioperative Morphine Analgesia in Children (PPMA), Cincinnati Genomic Control Cohort (CGCC) and Better Outcomes for Children (BOfC). The PPMA was conducted to identify genomic associations with morphine [33–35] and codeine response [29].

The CGCC collected biologic materials, including DNA samples, from healthy children living in the Cincinnati area to serve as control data for future studies. BOfC is a medical center biobank that stores children's left-over clinical samples for research purposes. Parents in all three studies gave consent to be contacted for future studies and/or to learn clinically relevant research results about their children. Only one parent per child was enrolled in the current study.

We mailed study invitation letters to all parents of children enrolled in the PPMA, CGCC and a random sample in the BOfC. To be eligible for participation, parents needed to be the biological or legal guardian of the child and the child had to be younger than 18 years. One month after the original mailing, we called or mailed follow-up letters to nonresponders. Parents interested in participating were told to contact the study coordinator by e-mail or phone to learn more about the study.

Informed consent was conducted via phone. Parents were considered enrolled when we received their signed and dated consent form. If we did not receive the signed consent form, parents were not contacted again. Parents were defined as cases if they reported that their child had a history of exposure to a prescribed opioid (ever been prescribed morphine, codeine, tramadol, oxycodone (Percocet/Percodan), hydrocodone, (Vicodin, Lortab), oxymorphone or hydromorphone (Dilaudid)). Parents were defined as controls if they reported that their child was naive to prescribed opioids. We estimated 98 participants in both the exposed and unexposed groups to detect a 20% difference in proportions with 80% power and a type 1 error rate of 5%. The study was approved by Cincinnati Children's Hospital Medical Center's (CCHMC) IRB.

CYP2D6 pharmacogenetics test

CYP2D6 was analyzed but not returned as part of the PPMA study. When signed consents were received from parents of children with DNA stored as part of CGCC or BOfC, the necessary aliquot of DNA was obtained for *CYP2D6* testing. The same assays were used for all samples and all assays were performed in CCHMC's Clinical Laboratory Improvement Amendments (CLIA)-approved and College of American Pathologists (CAP)-certified Molecular Genetics Laboratory. A TaqMan assay was used to detect normal function alleles (*2, *2A), decreased function alleles (*9, *10, *17, *41) and no function alleles (*3, *4, *6, *7, *8, *11, *14, *15, *18, *19, *20, *40, *42, *44). A separate, long-range PCR assay was used for the full gene deletion, *5, and full gene duplication. The wild-type allele, *1, was the default when targeted variants were not identified.

Figure 1. Child's DNA stored in a biobank retrieved for the research study.

Result disclosure

To assure consistency in result messages, members of the study team from CCHMC and Boston Children's Hospital developed the scripts and pretested them with friends, and family members without specialty training in genetics. The scripts contained descriptive language rather than scientific diplotype and predicted phenotype terms. Parents were told the number of *CYP2D6* genes their child had that make normal enzyme, make enzyme that may not work as well as expected or that do not make enzyme. This was followed by an explanation about how codeine might work to reduce the child's pain and whether or not the child was at an increased risk for side effects. Parents who were told their child had two *CYP2D6* genes that do not make enzyme or at least three *CYP2D6* genes that work well were told that their child's doctor should not prescribe codeine for their child based on national guidelines. Two children had indeterminate genotypes because they were compound heterozygotes and also had a duplication. The script indicated that it was not possible to predict how well codeine might work to lower pain nor whether or not the child was at increased risk for side effects from codeine. Responses from these two parents were excluded from further analyses. The script was written at a 7th grade level.

To better understand the impact of the returned result on perceived utility and sharing behaviors, we further categorized the result messages for data analysis. If the script indicated that based on national guidelines the child should not be given codeine, the result message was categorized as 'do not give.' If scripts stated the child had 'two *CYP2D6* genes that fully work' and that 'a normal dose of codeine should work to lower pain,' the result message was categorized as 'should work.' If scripts stated 'less [codeine] may be broken down to morphine' and if codeine does not help to lower pain to 'ask the doctor if a different pain medicine can be prescribed,' the result message was categorized as 'may not work as well.'

All results were disclosed by phone by an advanced practice registered nurse with training in genetics. Participants were given the opportunity to ask questions about the result and were told they would receive a copy of the result via mail.

Baseline & follow-up questionnaires

Immediately following result disclosure, a different study team member administered a baseline questionnaire via phone to assess parents' reactions to the results and parents' reported likelihood of sharing their child's *CYP2D6* pharmacogenetics test result with the child's doctor, pharmacist or the child.

Follow-up phone surveys were administered at 3 and 12 months to assess if and with whom parents shared their child's *CYP2D6* test results. Sharing questions to which a parent responded 'yes' at 3 months were not repeated at 12 months. For example, if a parent indicated at 3 months they had shared results with the child's doctor but not the pharmacist or child, only questions about sharing with the pharmacist or child were repeated at 12 months. Study procedures involving data collection are outlined in Figure 2. Participant responses were entered into a REDCap database during the phone surveys.

The study team modified a questionnaire previously administered by phone for a national pharmacogenetics study [36]. Data from five sections of the modified baseline questionnaire and one section of the follow-up questionnaires are considered in this study. The five baseline sections include: verification of child's opioid exposure status, self-reported demographic questions, the child's experience with prescribed medicines, parents' perceived utility (perceptions as to whether the parent or child's doctor could use the *CYP2D6* pharmacogenetics result to improve care for the child), and reported likelihood of sharing the result with the child's doctor, pharmacist and child. Response options for perceived utility questions were strongly agree, somewhat agree, somewhat disagree and strongly disagree. Response options for likelihood to share results were extremely likely, somewhat likely, not very likely and not at all likely. The baseline questionnaire was

pretested with family and friends of the interviewers for comprehension, ease of administration and amount of time to administer the survey. We contacted parents at 3 and 12 months by phone to ask if they had shared the results with the child, the child's primary care provider or the pharmacist. If parents indicated they had shared the results at either time period, they were counted as having shared the results. We also asked parents for permission to share the results with the child's primary care provider at 3 months. If parents were not reached at 3 months but were reached at 12 months, we asked for permission to share results at 12 months.

Statistical analysis

All the data were stored in a REDCap database. Statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute Inc., NC, USA). Demographic variables and past medication experiences were compared between cases and controls using Fisher's exact tests for frequencies and Wilcoxon rank-sum test for medians. We examined eight outcome variables, including parents' agreement that the test could be used by themselves or the child's doctor to improve care for the child, parents' likelihood of sharing results with the child's doctor, pharmacist and the genotyped child, and actual sharing of results with the child's provider, pharmacist and the genotyped child. Associations of exposure status, result message, child's age, parent's education, child's health and questionnaire-specific variables with outcome variables

Figure 2. Study procedures.

Table 1. Participants' characteristics.

Demographics	Unexposed (controls), n = 63	Exposed (cases), n = 91	p-value
Parent age (years), median (IQR)	46.0 (42.0, 50.0)	39.0 (35.0, 46.0)	<0.001
Child age (years), median (IQR)	14.0 (12.0, 16.0)	11.0 (7.0, 15.0)	<0.001
Respondent, n (%)			0.08
– Father	0 (0%)	6 (7%)	
– Mother	63 (100%)	85 (93%)	
Race, n (%)			0.79
– Black	2 (3%)	4 (4%)	
– Other	1 (2%)	4 (4%)	
– White	60 (95%)	83 (91%)	
Parent education, n (%)			0.33
– <12th grade	12 (19%)	11 (12%)	
– <4 years college	39 (62%)	55 (60%)	
– >College	12 (19%)	25 (27%)	
Overall health of child, n (%)			<0.001
– Excellent	51 (81%)	47 (52%)	
– Good	11 (17%)	30 (33%)	
– Bad (fair or poor)	1 (2%)	14 (15%)	
Result message, n (%)			0.44
– Should work	19 (30%)	35 (38%)	
– May not work as well	42 (67%)	51 (56%)	
– Do not give	2 (3%)	5 (5%)	

Ages are compared using the Wilcoxon rank-sum test; other variables are compared using Fisher's exact tests.
IQR: Interquartile range.

were examined by univariate analyses using Spearman's rank correlation coefficient. These variables were also examined by logistic (for binary responses) and ordinal logistic regressions (for three or more ordinal responses), in which exposure status, result message and significant variables ($p < 0.05$) identified from the univariate analyses were tested simultaneously. In the regression models, result message, parent's education and child's health status were tested as nominal or ordinal variables. Result message and child's health showed ordinal effects, while parent's education did not. Therefore, result message and child's health were treated as ordinal, while parent's education as nominal in the final models. Final regression models included exposure status, result message and variables remaining significant in regression analysis. Missing values were excluded. We report uncorrected p-values and used 0.05 as the cutoff for statistical significance.

Results

Study participants

The baseline survey was completed by 154 parents (91 cases and 63 controls). The distribution of

participants enrolled from each IRB protocol is described in Figure 1. The 3- and/or 12-month survey was completed by 134 parents (76 cases and 58 controls; Figure 1). Most participants were white mothers with at least some college education. The median ages of parents and their children in the control group were significantly higher than that of cases. Parents in the control group were also significantly more likely to report that their child was in excellent health compared with cases. Parental race, education and result messages did not differ between cases and controls (Table 1). Cases were significantly more likely than controls to report their child had a side effect from a prescribed medicine ($p = 0.001$) or stopped giving a prescribed medicine because it was not helping their child ($p = 0.001$). Cases were also more likely to have family members who stopped taking a prescribed medicine because it did not help their condition ($p = 0.03$; Table 2).

Univariate analyses

In addition to exposure status (Table 3), result message was the variable most frequently associated with

perceived utility, likelihood of sharing and actual sharing of *CYP2D6* results. Results from all univariate analyses are reported in [Supplementary Tables 1–8](#).

Perceived utility

All but one participant strongly agreed (n = 120) or agreed (n = 33) that they could use the research result to improve how they cared for their child. All participants strongly agreed (n = 130) or agreed (n = 24) that their child’s doctor could use the research result when providing care to the child. Proportionally more cases (84%) than controls (70%) strongly agreed that they could use the results to improve how they

cared for their child. Although not statistically significant, proportionally more cases (89%) than controls (78%) strongly agreed that the child’s doctor could use the research result when providing care to the child ([Table 3](#)).

In multiple regression analysis, parental agreement that results could be used to improve how the parent cares for the child was significantly associated with exposure and result message (p = 0.022 and 0.009, respectively; [Table 4](#)). Likewise, agreement that the doctor could use the result when providing care for the child was significantly associated with exposure and result message (p = 0.041 and 0.039; [Table 4](#)).

Table 2. Experience with prescribed medicines.			
Parents’ responses about child’s and family’s experiences with prescribed medicines	Control (n = 63), n (%)	Case (n = 91), n (%)	p-value
Has [child] ever had any type of side effect from a prescribed medicine?			0.003
– Yes	19 (31%)	51 (56%)	
– No	43 (69%)	40 (44%)	
If yes, have you ever stopped giving [child] a prescribed medicine because of the side effects?			0.33
– Yes	13 (68%)	42 (82%)	
– No	6 (32%)	9 (18%)	
Have you ever stopped giving [child] a prescribed medicine because it was not helping his/her condition?			0.001
– Yes	8 (14%)	33 (40%)	
– No	49 (86%)	49 (60%)	
Have any immediate family members (parents, children, sibling) ever stopped taking a prescribed medicine because of the side effects?			0.61
– Yes	31 (52%)	46 (57%)	
– No	29 (48%)	35 (43%)	
Have any immediate family members (parents, children, sibling) ever stopped taking a prescribed medicine because it did not help their condition?			0.025
– Yes	18 (29%)	39 (48%)	
– No	44 (71%)	42 (52%)	
Is [child] currently taking any type of prescribed medicine for a long-term or ongoing condition?			0.10
– Yes	24 (38%)	47 (52%)	
– No	39 (62%)	44 (48%)	
Is [child] taking any prescribed medicines to treat behavior problems or mental health problems like depression or bipolar disorder?			0.48
– Yes	7 (11%)	15 (16%)	
– No	56 (89%)	76 (84%)	
Data are compared using Fisher’s exact tests.			

Table 3. Perceived utility, likelihood of sharing and actual sharing between controls and cases.			
	Control (n = 63), n (%)	Case (n = 91), n (%)	p-value
Perceived utility[†]			
I can use this CYP2D6 research test result to improve how I care for [child]			0.037
– Strongly agree	44 (70%)	76 (84%)	
– Agree	18 (29%)	15 (16%)	
– Somewhat disagree	1 (2%)	0 (0%)	
[Child's] doctor can use this CYP2D6 research test when providing care to [child]			0.07
– Strongly agree	49 (78%)	81 (89%)	
– Agree	14 (22%)	10 (11%)	
Likelihood of sharing			
How likely are you to share [child's] CYP2D6 research test result with his/her doctors?			0.047
– Extremely likely	42 (67%)	74 (81%)	
– Somewhat likely	19 (30%)	15 (16%)	
– Not very likely	2 (3%)	2 (2%)	
– Not at all likely	0 (0%)	0 (0%)	
How likely are you to share [child's] CYP2D6 research test result with the pharmacist where you have your prescription drugs filled?			0.45
– Extremely likely	12 (19%)	26 (29%)	
– Somewhat likely	30 (48%)	34 (38%)	
– Not very likely	16 (25%)	24 (27%)	
– Not at all likely	5 (8%)	6 (7%)	
How likely are you to share [child's] CYP2D6 research test result with [child] in the next year?			0.06
– Extremely likely	30 (49%)	39 (43%)	
– Somewhat likely	18 (30%)	16 (18%)	
– Not very likely	8 (13%)	10 (11%)	
– Not at all likely	5 (8%)	26 (29%)	
Actual sharing at 3 or 12 months	Control (n = 58)	Case (n = 76)	p-value
Shared [child's] CYP2D6 research test result with [child's] primary care provider			0.048
– Yes	10 (17%)	25 (33%)	
– No	48 (83%)	51 (67%)	
Shared [child's] CYP2D6 research test result with pharmacist			0.69
– Yes	2 (3%)	4 (5%)	
– No	56 (97%)	70 (95%)	
Shared [child's] CYP2D6 research test result with child			0.19
– Yes	30 (64%)	36 (51%)	
– No	17 (36%)	35 (49%)	
The association between case/control and outcome responses was assessed using Spearman's correlation.			
[†] Response options: Strongly agree, agree, somewhat disagree, strongly disagree. Responses options not selected are not shown.			

Sharing results with doctor

Nearly all participants (97%) reported that they were extremely or somewhat likely to share the *CYP2D6* research results with the child's doctor. A higher proportion of cases (81%) than controls (67%) reported being extremely likely to share the results with the child's doctor ($p = 0.047$). At follow-up, 26% of those reached reported that they had shared results with the child's primary care provider. Cases were more likely than controls to report sharing the results with the child's provider at 3- or 12-month follow-up ($p = 0.048$; Table 3).

In regression analysis (Table 4), likelihood of sharing results with the child's doctor was associated with exposure ($p = 0.042$), result message ($p < 0.001$), child age ($p = 0.022$) and parent education ($p = 0.016$). The odds of being likely to share with the child's doctor among cases was 2.5-fold that of controls. There was a linear increase in the odds of being likely to share with the type of result message returned. The odds of being likely to share with the doctor among parents who received a 'may not work as well' result message was 7.3-fold that of parents who received a 'should work' result message, and was 53.3-fold higher among parents who received a 'do not give' result message versus a 'may not work as well' result message. The odds of being likely to share with the child's doctor increased by 1.1 with a 1-year decrease in child age. Finally, parents with a 12th grade education or less were more likely to share compared with parents with some college or a college degree (odds ratio [OR] = 5.3), and parents with more than 4 years of college (OR = 10.4), while no difference was detected between parents with some college or a college degree and more than a college degree.

Only opioid exposure ($p = 0.026$) and result message ($p = 0.030$) were associated with actually sharing results with the child's provider in regression analysis (Table 4).

After collecting data about actual sharing, we asked 111 parents for permission to share the *CYP2D6* laboratory report with the child's provider at 3 ($n = 102$) or 12 months ($n = 9$). Nearly all parents gave permission ($n = 105$; 95%).

Sharing results with pharmacist

The majority of participants (67%) were extremely or somewhat likely to share *CYP2D6* results with the pharmacist. Likelihood of sharing with the pharmacist did not significantly differ between cases and controls (Table 3). In regression analysis, only result message ($p = 0.001$) was associated with parent's likelihood of sharing results with the child's pharmacist (Table 4).

At follow-up, six participants reported actually sharing their child's *CYP2D6* research result with a pharmacist. Actual sharing with the pharmacist did not differ among cases and controls (Table 3). Only result message ($p = 0.037$) was found to influence actual sharing of results with the pharmacist in regression analysis (Table 4).

Sharing results with child

Most participants (67%) were extremely or somewhat likely to share results with their child in the next year. Although not significant, likelihood of sharing results with the child in the next year was higher among controls than cases ($p = 0.06$; Table 3). In regression analysis, neither exposure nor result message was associated with likelihood of sharing results with the child. However, age of the child and parental education were associated with likelihood of sharing results with the child in the next year in regression analysis (Table 4). In regression analysis, age was associated with likelihood of sharing with the child in an exposure-specific manner ($p = 0.03$). The odds of being likely to share results with the child in the next year increased by 1.4 (95% CI: 1.3–1.6) with each year of age among cases, while in controls, the odds only increased by 1.2 (95% CI: 1.0–1.4). Parental education was also associated with likelihood of sharing results with the child in the next year in regression analysis ($p = 0.034$). Compared with parents with postgraduate education, the odds of sharing with the child by parents with some college and less than or equal to a 12th grade education were 2.6 (95% CI: 1.2–5.6) and 2.9 (95% CI: 0.9–9.2)-fold higher, respectively.

Nearly half (49%) of the parents reported actually sharing results with their child during one of the follow-up calls. Opioid exposure was not associated with sharing (Table 3). Older age of the child ($p < 0.001$) was the only variable found in regression analysis to be associated with actually sharing the result with the child (Table 4).

Child's health & opioid exposure

In our cohort, child health significantly differed between cases and controls (Table 1), and univariate tests detected marginal association of child health with parents' actual sharing with the child's doctor and with the child (Supplementary Tables 4 & 8). Therefore, the potential confounding effect of child health was tested. When included in multiple regression models, child health was not significantly associated with any of the outcome variables. Furthermore, we stratified analyses by child health or opioid exposure. For perceived utility and sharing results with the child's doctor (likely and actual), opioid exposure status showed consistent

Table 4. Variables associated with perceived utility, intent to share and actual sharing in regression analysis.

Utility/sharing	Outcome	Significant independent variable		
		Variable	OR (95% CI)	p-value
Perceived utility	Parent can use	Case-control		0.022
		– Control	Reference	
		– Case	2.5 (1.1–5.6)	
		Result message		0.009
		– Should work	Reference	
		– May not work as well	2.7 (1.3–5.7)	
		– Do not give	7.1 (1.6–32.5)	
	Doctor can use	Case-control		0.041
		– Control	Reference	
		– Case	2.5 (1.0–6.3)	
		Result message		0.039
		– Should work	Reference	
		– May not work as well	2.4 (1.0–5.6)	
		– Do not give	5.8 (1.1–31.9)	
Sharing results with doctor	Likely	Case-control		0.042
		– Control	Reference	
		– Case	2.5 (1.0–6.1)	
		Result message		<0.001
		– Should work	Reference	
		– May not work as well	7.3 (3.1–17.3)	
		– Do not give	53.3 (9.5–298.1)	
		– Child age (1 year younger)	1.1 (1.0–1.3)	0.022
	Actually	Parent education		0.016
		– ≤12th grade	10.4 (1.7–64.3)	
		– ≤4 years college	2.0 (0.7–5.2)	
		– ≥College	Reference	
		Case-control		0.026
		– Control	Reference	
		– Case	2.6 (1.1–6.0)	
		Result message		0.030
		– Should work	Reference	
		– May not work as well	2.2 (1.1–4.5)	
		– Do not give	4.7 (1.1–20.1)	
Sharing results with pharmacist	Likely	Result message		0.001
		– Should work	Reference	
		– May not work as well	2.5 (1.4–4.4)	
		– Do not give	6.3 (2.1–19.4)	

Variables exposure status, result message and variables significant in univariate analyses were tested simultaneously. Final models include exposure status, result message and variables remaining significant in regression analysis. Only significant values are shown. OR: Odds ratio.

Table 4. Variables associated with perceived utility, intent to share and actual sharing in regression analysis (cont.).				
Utility/sharing	Outcome	Significant independent variable		
		Variable	OR (95% CI)	p-value
Sharing results with pharmacist (cont.)	Actually	Result message		0.037
		– Should work	Reference	
		– May not work as well	4.9 (1.0–22.7)	
		– Do not give	23.5 (1.1–516.0)	
Sharing results with child	Likely	Exposure × child age (1 year increments)		0.024
		– Child age (controls)	1.2 (1.0–1.4)	
		– Child age (case)	1.4 (1.3–1.6)	
	Likely	Parent education		0.034
		– ≤12th grade	2.9 (0.9–9.2)	
		– ≤4 years college	2.6 (1.2–5.6)	
		– ≥College	Reference	
	Actually	Child age (1 year older)	1.4 (1.2–1.5)	<0.001
Variables exposure status, result message and variables significant in univariate analyses were tested simultaneously. Final models include exposure status, result message and variables remaining significant in regression analysis. Only significant values are shown. OR: Odds ratio.				

impact on the outcomes when child health was stratified, while no impact of child health was detected when cases and controls were analyzed separately. These results suggest that opioid exposure status was a more important factor than child’s health in influencing parents’ perceived utility and likelihood of and actual sharing of results with the child’s doctor.

Discussion

Clinical actionability is supported by researchers and clinicians as a rationale for returning individual research results [37,38]. Established clinical utility of a result is oftentimes necessary before a result’s actionability is considered by a research team. In addition, considerations of actionability may vary by the patient population being studied. This study is the first to examine parent’s perceived utility and sharing behaviors related to their child’s pharmacogenetics research result. Consistent with our hypotheses, parents of children previously exposed to opioids were more likely than parents of children not previously exposed to opioids to strongly agree that they or their child’s doctor could use the results to improve care for the child (perceived utility). Cases were also more likely than controls to report higher likelihood of sharing results with their child’s doctor and to report that they actually shared the results within 12 months of receiving them. Result message was associated with perceived utility, likelihood of sharing and actual sharing of

results with the child’s doctor and pharmacist. However, only older age of the child was associated with likelihood of sharing results with the child in the next year in regression analysis.

Previous research indicates that adult patients, consumers and research participants who experienced pharmacogenetics testing valued it [39–41]. However, none of these studies focused on a pediatric population and only one specifically explored reactions to receiving *CYP2D6* results [41]. To our knowledge, our study is the first to find that parents value receiving their child’s pharmacogenetics research results and feel the results will be useful to them and their child’s doctor. We intentionally chose to return *CYP2D6* within the context of the gene result’s implications for opioid response as nearly 3% of children will be prescribed an opioid for pain management and the most common prescriptions are for codeine, hydrocodone and oxycodone [26]. Other investigators chose to return *CYP2D6* research results by mail to over 1000 adult participants. The mailed result message focused on describing the participant’s genotype predicted metabolism phenotype without specific therapeutic recommendations. A common suggestion by participants to improve the general *CYP2D6* results was to offer specific information to help them manage their care [42].

Because opioids are prescribed during childhood, we were able to test whether or not a child’s prior experience with an opioid influenced parents’

perceived utility of the research result. Past experience has been shown to be an important context within which research participants judge meaning of a result [43]. Our findings indicate previous opioid exposure and result message influenced both likelihood of sharing and actual sharing with the child's doctor. Others have found that patients and consumers who experienced ADRs showed greater interest in or support of pharmacogenetics testing [44,45] and that high pharmacogenetics risk was associated with more physician visits [40]. Evidence-based guidelines exist for many pharmacogenetics tests [5]. Given the expectation and interest in return of pharmacogenetics research results [8,41], as well as our findings that parents' perceive the results to be clinically useful and intend to share them with their child's provider, return of pharmacogenetics research results for which clinical guidelines exist is warranted. However, if the proportion of research participants who share clinically actionable research results with healthcare providers is low or varies by exposure, it is important for investigators to consider the return of results to providers as well as participants. While return of results in a research setting is not clinical practice, it has been proposed that the hand-off between research and clinical care can be accomplished in some cases by engaging research participants' healthcare providers [37].

Research participants' permission is an important factor on which to base decisions about return of research results to healthcare providers. Although likelihood of sharing results with the child's doctor was higher in our study than that reported in a study of 62 mothers prescribed codeine (97 vs 60%) [41], only slightly more than a quarter of participants in our study had actually shared the results with the child's doctor within 12 months of receiving them. This discrepancy between likelihood of sharing and actual sharing could be because most parents gave the study team permission to send the *CYP2D6* results to the child's doctor and thus may have felt that the results had already been or would be shared. However, we did not ask permission to share the *CYP2D6* results until the first follow-up call with the participant at either 3 or 12 months. An alternative explanation could be that the parents had not yet taken their child to a medical visit by the time we followed-up with them. Although we did not ask about the number of medical visits since return of the child's *CYP2D6* results, cases reported sharing the results with the child's doctor more often than controls, perhaps because cases have more medical visits than controls and, therefore, more opportunities to share results. A number of findings

associated with opioid exposure suggest a need for more frequent medical visits among cases, including poorer reported health, higher likelihood to have had a side effect from a prescribed medicine or stopping a medication because it was not helping the child's condition. Younger age of the child may have been associated with actual sharing with the child's doctor simply because younger children have more medical visits than older children [46,47].

While nearly all parents reported being likely to share results with the child's doctor, only two-thirds reported they were likely to share results with the pharmacist where they have their prescriptions filled. Result message was the only variable associated with both likelihood of sharing and actual sharing with the pharmacist in regression analysis. However, only six parents reported at follow-up that they had actually shared results with the pharmacist where they fill prescriptions. Parents may be less likely to have an ongoing relationship with a pharmacist than with a physician and thus may be less likely to ask the pharmacist medical questions. Also, when filling prescriptions, parents may not interact directly with the pharmacist, but with an assistant or technician. Pharmacists may increasingly play a role in offering and communicating results from pharmacogenetics testing. Since results from pharmacogenetics testing may have relevance to medication management therapy for more than one prescribed medication, and since multiple prescribers may be involved in managing the health of the same patient, pharmacists could be central to communicating with patients about the implications of pharmacogenetics testing. At least one pilot study with five community pharmacies found it feasible for pharmacists to offer pharmacogenetics testing in terms of pharmacist time and patient interest, however, additional training to improve result interpretation was recommended [48]. Hospitals have also implemented pharmacist-managed pharmacogenetics services [49]. However, in addition to education about result interpretation, additional challenges include reimbursement for testing and pharmacists consults [49,50] as well as access to pharmacogenetics test results in community pharmacy settings [51]. In our study, return of results directly to research participants facilitated little sharing of pharmacogenetics test results with pharmacists, suggesting alternative mechanisms of result communication may be needed if pharmacists are to be involved in pharmacogenetics test interpretation.

We saw the most consistency between reported likelihood of sharing and actual sharing of *CYP2D6* results with the child (68 and 56%, respectively). However, neither exposure nor result message was

associated with likelihood of sharing or actual sharing of results with the child. Older age of the child was a stronger predictor of likelihood of sharing and the only variable associated with actual sharing of the result with the child in regression analysis. This finding is not surprising given that older children are likely better able to understand the *CYP2D6* results than younger children. Developmental stage and maturity of the child has been found to influence when parents share genetic information about Mendelian conditions. Specifically, parents considered what information their children could handle and how much their children needed to know [52,53] when deciding what to disclose and when.

Interpretation of clinical actionability of results obtained in a research setting may vary among healthcare providers, researchers, laboratories and institutional review boards. However, the practical, legal and ethical differences between research and medical practice must be considered [37]. Evidence-based guidelines are one standard on which to base decisions about return of research results to participants and their healthcare providers.

Limitations

Participants were primarily white women with at least some college education. All had previously participated in research studies. Exposure status was self-reported by most participants and could have resulted in some misclassification. As noted, cases reported poorer health than controls, possibly because of the sources

of recruitment. More controls were recruited from a healthy cohort, whereas more cases came from a hospital biobank and a study about pain. However, poorer health was not associated with perceived utility or sharing behaviors. We did not correct for multiple analyses, however, trends in significance were consistent across outcomes.

Conclusion

Our results suggest that parents perceive their child's *CYP2D6* research results to be useful and that prior opioid exposure influenced reported likelihood of sharing and actual sharing of results with the child's doctor but not the child. While guidelines do not suggest that *CYP2D6* testing should routinely be performed, guidelines do provide recommendations regarding medications selection if such results are available [21,22]. Genomic research studies considering return of research results for children should offer return of pharmacogenetics results that can be supported by gene–drug guidelines containing therapeutic recommendations. Although only about a third of participants had actually shared results with the child's provider within 12 months of receiving them, permission for the study team to share the results with the child's provider was high. Thus, nearly all providers caring for the children in our study received *CYP2D6* research results. How providers respond to such information and whether they integrate clinical guidelines in medication selection going forward is unknown.

Summary points

- Genomics researchers are beginning to explore how return of actionable genetic variants to patients and clinicians impacts clinical care and health outcomes.
- Guidelines with therapeutic recommendations based on pharmacogenetics results exist suggesting that pharmacogenetics findings may increasingly be considered returnable if identified in genomic research studies.
- There is little information regarding parents' responses to their child's pharmacogenetics research results. Prior to our study, no information could be found in the literature regarding how a child's past exposure to prescribed pain medication influences a parent's intended and actual sharing of pharmacogenetics test results.
- We sought to determine whether perceived utility of *CYP2D6* research results differed between parents whose children had a history of exposure to a prescribed opioid (cases) and parents whose children had no history of exposure to a prescribed opioid (controls). We also sought to determine parents' reported likelihood of sharing, and actual sharing of their child's *CYP2D6* research result with their child's doctor.
- The child's prior opioid exposure was positively associated with parents' perceived utility of *CYP2D6* research results, likelihood of sharing results with the child's doctor, and actual sharing of results with the child's doctor.
- Exposure status was not associated with likelihood of sharing or actual sharing of results with the child or the child's pharmacist.
- Only older age of the child was associated with likelihood of sharing results with the child in the next year.
- Genomic research studies considering return of research results for children should offer return of pharmacogenetics results that can be supported by gene–drug guidelines containing therapeutic recommendations.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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