Inconclusive genetic test results for osteogenesis imperfecta in children with unexplained fractures - current practice and the provider perspective

Emily Youngblom

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2014

Committee:

Mitzi L. Murray

Kelly Edwards

Program Authorized to Offer Degree:

School of Public Health- Genetics

University of Washington

Abstract

Inconclusive genetic test results for osteogenesis imperfecta in children with unexplained fractures - current practice and the provider perspective

Emily Youngblom

Chair of Supervisory Committee:

Kelly Edwards

Bioethics and Humanities

Institute for Public Health Genetics (IPHG)

Background: In children with unexplained fractures, healthcare providers often must consider whether the etiology is non-accidental injury (NAI) or an underlying predisposition to bone fractures, such as osteogenesis imperfecta (OI). Genetic testing may be variably used to address this question and uncertainty can be introduced if the results are inconclusive.

Methods: Physicians in the Collagen Diagnostic Laboratory database at the University of Washington were sent a 15 question survey to gather information regarding their utilization of genetic test results for OI when their patient was suspect of NAI.

Results: Results from 89 participants indicate that there exists differential practices in regards to the following: when genetic testing should be ordered for OI vs. NAI cases, who should be consulted and which additional procedures are required for follow-up analysis of a variant of uncertain significance, and to whom the genetic results should be released.

Conclusion: Differences in practice raise ethical concerns about whether these differences are justified, and how they can be addressed. Information from the study can inform changes in policy and education to eliminate some of the disparities and alleviate some ethical concerns.

Introduction

This research focuses on one way that genetic information is used by the legal system: genetic testing for the group of heritable disorders called osteogenesis imperfecta (OI). OI is characterized by unexplained skeletal fracture(s), and thus can occasionally be confused with fractures due to non-accidental injury (NAI), or child abuse. In recent years, results for the genetic test for OI have been used by the legal community to help determine whether or not a child has a genetic predisposition for otherwise unexplained fractures[1, 2]. For example, in a county case in England in 2011, a couple accused of abusing their children after taking their 6-week old son to the hospital. Social services were called in, and both children were placed in foster care. The couple was arrested for child abuse and permitted to see their children for only six hours a day under direct supervision. Two months after they were removed from their children, the couple got divorced due to the strain of the situation. After 18 months, a physician suggested that the children may have OI, which subsequent testing confirmed. Other similar cases are documented[3, 4].

Thus far, little research has been done on this particular application of OI genetic testing, so this research project was designed to help fill in knowledge gaps concerning the ethical, legal, and social implications (ELSI) of using genetic testing in cases in which NAI is of concern in a child with unexplained fractures.

Advances in genetic technology and understanding of the role of genetic factors in human health continue to increase at an exponential rate[5]. Today, genetics and genomics influence many aspects of our daily lives, whether we realize it or not[6]. The hope of using genetic information to benefit health has long been accompanied by social, legal and ethical concerns surrounding use of that information. Genetic information has been used in courts since 1986, when it was first used to exonerate an English man accused of two rape-murders[7]. Since then, the use of DNA

testing in courts has been increasing. Parental testing is commonly used in family court and identity testing is applied in criminal courts in forensic investigations for the purpose of identifying victims, identifying or excluding suspects and even in exonerating convicted but innocent individuals. On the 30th of October 2004, President George Bush signed the Justice for All Act, which heightened both funding and guidelines for the use of DNA technology in the judicial process[8].

In addition to parental and identity testing, genetic testing may be used to investigate whether a genetic diagnosis is present in a victim or suspect that is relevant to an ongoing investigation or legal proceeding. One such use is in investigating whether an unexplained bone fracture in a child is due to non-accidental injury (NAI) or attributable to a predisposition to bone fractures. Fractures in children are common, accounting for up to one-fourth of all pediatric injuries;[9] it is estimated that 18% of all children will have a fracture by age 9[10]. In children under 16 years of age, 1.3% of femur fractures were attributed to NAI, approximately 75% was attributed to falls or motor vehicle accidents, and a one-quarter are unexplained[11]. In the United States, there are approximately 581,000 cases of physical child abuse every year; prevalence of NAI with fractures is approximately 24:10,000 children in the birth to three year range (as of 2002)[12]. In 2004, in children less than 3 year old, 24%-40% of all fractures were suspected to be related to non-accidental injury[13 14 15 16]. However, an estimated 7% of children who have signs suggestive of NAI actually have an underlying medical condition that explains the observed bone fractures[17].

Osteogenesis imperfecta (OI) is a heritable (genetic) connective tissue disorder primarily characterized by increased risk of bone fractures[18]. Depending on the severity, other features of OI may include blue sclerae, bowing of the long bones, and short stature, but these are not always present in each case[Error! Bookmark not defined.Error! Bookmark not defined.]. A diagnosis of OI may

be considered when a child presents with unexplained fractures and a previous study showed the incidence of OI among children evaluated for NAI is 2–5%[Error! Bookmark not defined.Error! Bookmark not defined.]. The prevalence of OI (1:10,000 – 1: 20,000) is much less common than NAI, making NAI approximately 24 times more likely to be the cause of unexplained fractures[19 1]. Although it has been argued that certain types of fractures are most commonly seen in cases of NAI, this remains controversial. Moreover, given that all type of fractures can occur as a result of OI, it can be difficult to distinguish the cause(s) of the fractures[20 21] Many patients are referred for genetic testing for OI as a means to help rule out a genetic cause of unexplained fractures[1, Error! Bookmark not defined.Error! Bookmark not defined., Error! Bookmark not defined.Error! Bookmark not defined.]. If a test for OI in a child is negative, it is less likely that he or she has a genetic condition that would be contributing to the bone fractures, making NAI a more likely explanation. On the other hand, if genetic testing establishes a diagnosis of OI in a child, the unexplained fractures *may* be due primarily to the genetic condition. However, a diagnosis of OI does not exclude the possibility of NAI, as the two are not mutually exclusive.

There are many complexities when testing for genetic conditions, including OI. One such complexity is the locus heterogeneity of OI. This means that mutations (disease causing variants) in different unrelated loci (locations in the genome) can result in the same disorder. In OI, 90% of cases are due to a mutation in either *COL1A1* or *COL1A2*, the genes that encode type I procollagen. Over 500 different pathogenic mutations in these genes that cause the phenotype have already been identified[22 23]. Other genes in which mutations result in OI include the dominant gene *IFITM5*, as well as the following recessive genes: *BMP1, CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, SERPINH1, SP7, TMEM38B* and *WNT1*.

Another layer of complexity in genetic testing for OI is that the test results are not always conclusive. It is possible for a patient to have a variant in *COL1A1* and *COL1A2* whose clinical

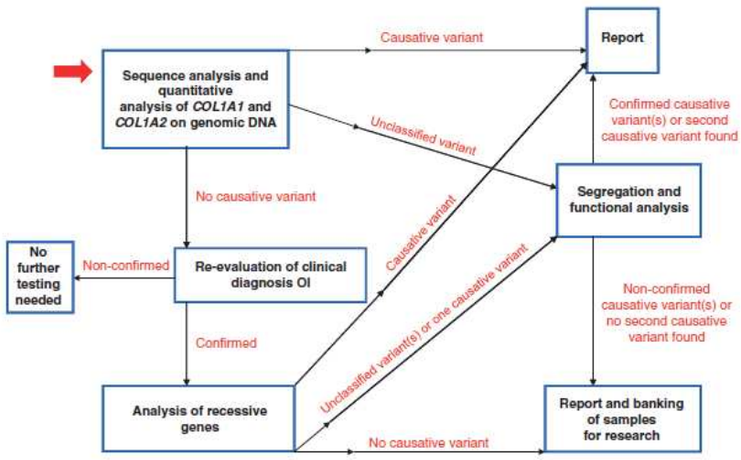
significance is unknown. This may be because the variant is novel, rare, or atypical for the type of alteration that usually gives rise to condition. In this case, the test is inconclusive and the clinicians are unable to determine if that variant is contributing to the bone fractures or not. A result of this type is aptly called a variant of unknown significance (VUS)[24]. Genetic test results for *COL1A1* and *COL1A2* that come back as inconclusive, or a VUS, are not uncommon. At the CDL Collagen Diagnostic Laboratory (CDL) at the University of Washington (UW), where this study was conducted, about 13% of all tests for *COL1A1* or *COL1A2* come back as VUS[25]. A VUS may be reclassified at a later date in time if further knowledge about the phenotypic effect of the variant is acquired. It may be then reclassified as one of the following: benign, likely benign, likely mutation, or mutation. There does not currently exist any regulation as to whether it is the responsibility of the provider to alert patients of change in VUS status, or if it is the responsibility of the patient to obtain the information themselves. Over time, the diagnostic accuracy of genetic tests for OI is certain to improve, as more information about the functionality of each variant is uncovered.

A misappraisal of the genetic evidence could have significant consequences on the family under investigation. In 46 states in the United States of America, children suspected to be victims of child abuse can be removed from their home without a court order by law enforcement if a clear and present danger to a child's health, safety, or welfare if suspected[26]. About 20 U.S. states give this same authority to Child Protective Services[27]. If an allegation of child abuse is determined to be founded, a child may be placed into state custody or foster care for protection. Alternatively, if there is a plausible medical explanation for the child's fractures, the child may be safely kept within the family and provided with appropriate medical care. The separation of a child and parents can cause a total disruption of the family, including a loss of familiar people and surroundings for the child, which may be traumatic[28]. While the determination of whether a

child has suffered physical abuse takes into account a variety of evidence, genetic test results can play a pivotal role[3]. For this reason, it is critical that information obtained through genetic testing for OI is properly utilized, which can be difficult given the complexities of the test previously described.

The European Molecular Genetics Quality Network (EMQN) recommends that *COL1A1* and *COL1A2* are studied first when a patient is evaluated for OI with genetic testing. If no mutation is identified and the patient is still believed to have a clinical diagnosis of OI, other genes, including the recessive genes previously mentioned, are subsequently tested[**Error! Bookmark not defined.Error! Bookmark not defined.**]. If an unclassified variant is found in *COL1A1* or *COL1A2*, segregation and functional analysis can be performed to help determine whether or not the unclassified variant is causative. Segregation analysis relies on genetic information from the patient's family members, particularly, the parents, to determine if a pathogenic mutation has been identified. For example, if one parent also has the same variant identified in the patient but the parent does not have frequent fractures, the probability that that variant is responsible for the frequent fractures in the child is minute. Not identifying a mutation in *COL1A1* or *COL1A2* makes the diagnosis of OI less likely but does not entirely exclude the diagnosis. Figure 1 from van Dijk et al.'s paper helps to illustrate this.

Figure 1. EMQN preferred diagnostic flow of OI[2]



While the testing algorithm may appear relatively straightforward, the social and legal implications of inconclusive or uncertain genetic test results can be challenging for providers, families and the legal system[29]. To date, the current practices surrounding genetic testing for OI in cases of unexplained fractures and the perspectives of various stakeholders involved is not well characterized, especially when the results of the testing are inconclusive. As the person often held responsible for informing the family and court as to whether there is a medical explanation for a child's unexplained fractures (such as OI), the healthcare provider plays a critical role. For this reason, this research study was undertaken to elicit relevant information regarding the practices surrounding genetic testing for OI in cases of unexplained fractures and the perspective of the providers that refer patients for testing, especially in cases where the test results are inconclusive.

Focus of Research

This research focuses on the ethical, legal, and social implications (ELSI) of genetic testing in cases in which non-accidental trauma is of concern in a child with unexplained

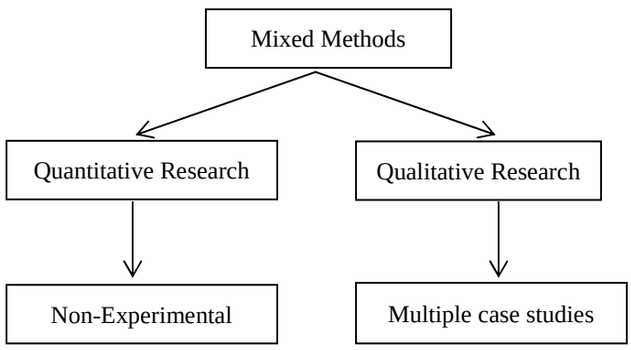
fracture(s). The primary research question seeks to understand the practices surrounding genetic testing in this scenario and provider perspectives surrounding identification of a VUS result. Due to the limited research that has so far been done on this particular topic, it is still unclear as to whether or not there exists a need for informational or educational changes, or modifications to policy or procedure in this area. Characterization of the way genetic tests for OI are currently being utilized and the provider perspective in this domain will help to indicate or better inform any potential need for change.

Methods

This study uses a mixed methods model, in which both quantitative and qualitative methods are used[30]. This type of study design was chosen because neither qualitative nor quantitative methods alone could adequately capture how providers and patients' family members interpret OI test results.

For the qualitative research, a multiple case study was the most logical option to allow for exploration of the differences within and between provider responses[3132]. For the quantitative research, a non-experimental approach was taken. Figure 2 illustrates this.

Figure 2: Mixed methods study design flowchart



This study was approved by the University of Washington Institutional Review Board (IRB) Minimal Risk Committee.

Study Setting

The Collagen Diagnostic Laboratory (CDL) is housed in the Department of Pathology at the University of Washington, in Seattle, Washington, USA. The laboratory is under the direction of Dr. Peter Byers and has offered clinical diagnostic testing for osteogenesis imperfecta for over 30 years.

Development of survey

A 15 item survey was developed collaboratively by the following members of the CDL at the University of Washington: Emily Youngblom, MPH, Melanie Pepin, MS, LGC, Mitzi L. Murray, MD, MA, and Dru Leistritz, MS, LGC. Questions were constructed to address key issues recognized from clinical experience and practice (Appendix 2). A combination of multiple choice, sliding scale bars, and short answer formats were utilized. An open textbox was

left at the end of the survey to allow for any additional comments or questions by participating physicians. The list of final questions (without answer choices) is shown in Table 1. The mean score for each of the questions related to frequency was calculated using the following values:

Always = 5

Often = 4

Sometimes = 3

Rarely = 2

Never = 1

The number of respondents that chose each frequency was multiplied by that choice's point value; the total score for each follow-up procedure was summed and divided by the total number of respondents to each procedure choice to find the mean score.

Table 1. List of final questions (without answer choices)

1. What is your specialty?

2. How often are you consulted to see patients for whom the differential diagnosis is osteogenesis imperfecta (OI) or non-accidental injury (NAI)? Please include those in which no genetic testing for OI is done.

3. If you suspect non-accidental injury in a patient, what features help you decide whether or not to order genetic testing for OI (*COL1A1/COL1A2* genes)?

4. What is your estimate of the percentage of your patients who are genetically tested for *COL1A1/1A2* are legal cases (child is put in foster care, charges are pressed against parents, case goes to court)?

5. After a patient's genetic test result for *COL1A1/1A2* comes back as a VUS, are any of the following procedures ever carried out as a next step?

6. After a patient's genetic test result for *COL1A1/1A2* comes back as a VUS, who typically recommends/requests the following procedures?

7. If the actions from the previous question are not carried out, what is the most common reason why not?

8. Of those patients whose results come back as a VUS in *COL1A1/COL1A2*, approximately what percentage of them return to clinic for follow-up of a possible diagnosis of OI?

9. When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in *COL1A1/1A2*, what are the most frequent reactions from the parents/guardians of the patient when you return the result?

10. In your experience, to whom are the results of OI vs. NAI genetic testing typically released, and approximately how often?

11. Of those patients whose results come back as a VUS in *COL1A1/1A2*, approximately what percentage of them are removed from their home without further testing?

12. When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in COL1A1/1A2, approximately what percentage of the time do you request help from a genetic counselor to interpret the results?

13. Displays if Q12 is Never: Why not?

14. For patients who receive a VUS test result, do you discuss with the parents/guardians any plans to keep them informed of any changes to the VUS status in the future?

15. Any additional comments on genetic testing for osteogenesis imperfecta vs. non-accidental injury?

Recruitment

Potential research subjects were identified through the CDL. Eligibility criteria were 1) providers who referred a patient for testing of *COL1A1* and *COL1A2* to the CDL between the 2005 and 2013; 2) the case referred for testing was a patient between the ages of birth and five years on suspicion of non-accidental injury (NAI) versus osteogenesis imperfecta (OI); 3) an active email address for the provider or the provider's genetic counselor was provided to the CDL or was listed in the American Society for Human Genetics (ASHG) database[33].

Physicians were recruited for research participation via an email that included an introduction to the study and a link to a survey hosted by Qualtrics (Survey Software Tool) (Appendix 1). In this email, we specified that "genetic testing for OI" refers only to testing for mutations in the *COL1A1* and *COL1A2* genes, which are responsible for about 90% of all OI cases.

All subjects were sent an identical survey. No identifying information was collected to ensure all responses were anonymous. All responses were compiled and tabulated by Qualtrics Survey Software, and were available to view either in aggregate, or as individual responses. Email invitations for study participation were sent once. If a subject did not respond, he or she was counted as a refusal, and not re-contacted.

Results

Of the 22,169 referring providers in the Collagen Diagnostic Laboratory (CDL) database, 580 had referred a child for genetic testing of *COL1A1* and *COL1A2* with a suspicion of NAI (as of April 2014). Of those, email addresses were obtained for 220 through the ASHG database and for 72 through the CDL. A total of 89 participants responded (81 in the ASHG group, 8 in the CDL group), yielding a recruitment rate of 30% (Figure 3). Sixty-seven respondents (23%)

completed every question in the study. Responses to individual questions were included in analysis regardless of whether or not the survey was completed. The subjects self-identified their practice specialty as neurology, genetics, pediatrics, or a combination of the three (Figure 4).

Figure 3. Flowchart of recruitment process and response rate

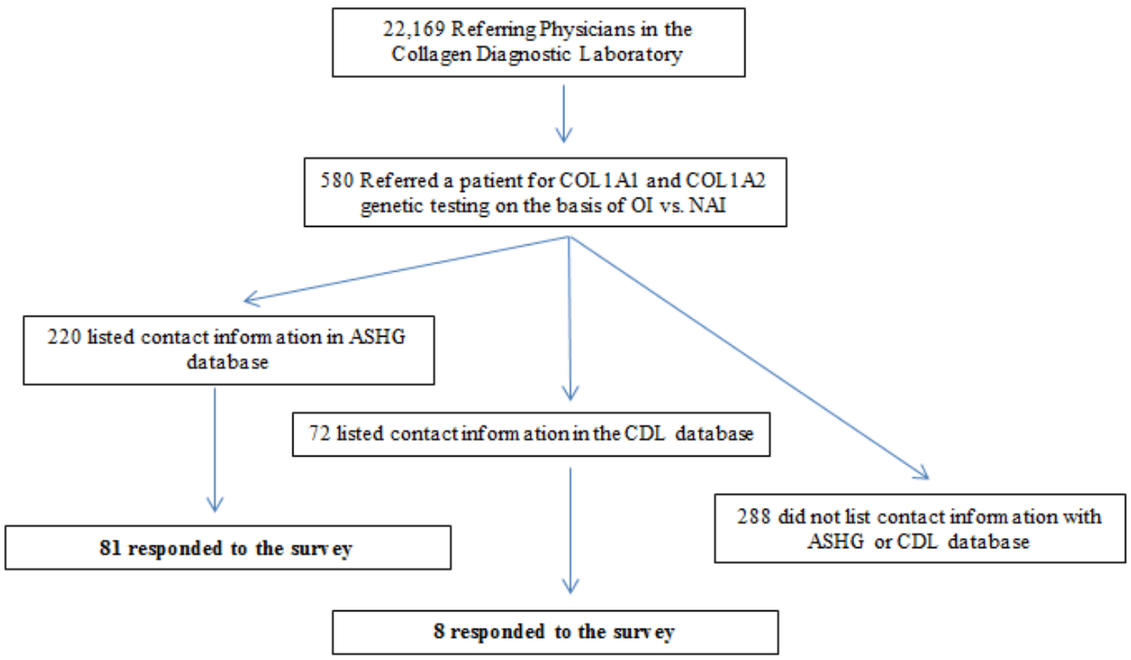
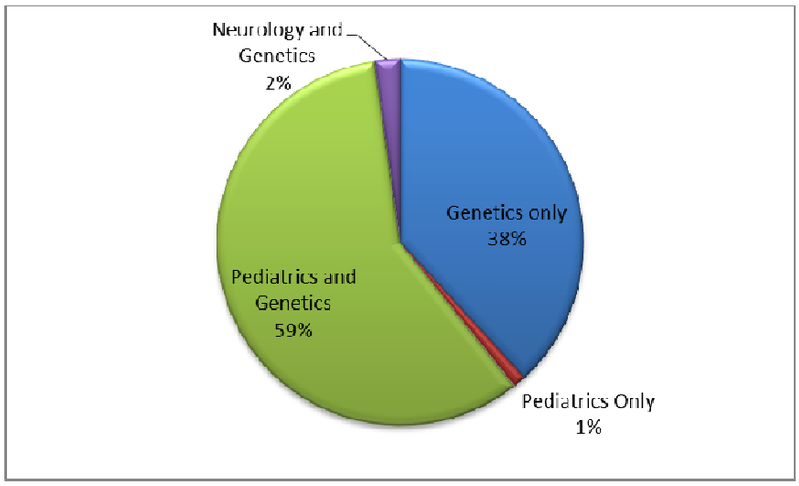


Figure 4 Specialty of recruited providers



Survey Results

Participants saw an average of 6.39 patients per year in which the differential diagnosis included OI and NAI, 36% of which were estimated to be legal cases. One participant replied that 100% of cases seen for this indication were prosecuted.

Contextual factors identified that influenced the decision as to whether to refer a patient for genetic testing include: other clinical features of OI (85%), family history of features of OI (76%), fracture number or type (74%), and social history of the child's family (35%). Examples of social history stated on the survey included patient's living arrangement, parents' occupations, and parents' criminal records. Additional factors identified by respondents that influence the decision surrounding testing are as follows: one participant would order genetic testing if the fractures continued once the child was removed from the home or the suspected perpetrator; one participant would hold an interview with caregivers (usually parents) to determine consistency of patient's history with OI diagnosis; and along the same lines, a different respondent would order genetic testing anytime there is an absence of a confession of NAI. All patients under investigation for possible non-accidental injury were referred for testing under protocol of their

institution by 13% of respondents. One respondent always orders genetic testing because a confirmation of NAI does not rule out OI as a possible diagnosis; similar sentiments that the two diagnoses are not mutually exclusive came up twice in open comments at the end of the survey.

When asked if they had any further comments on genetic testing for OI, one participant wrote, “it seems that there are no guidelines as to when to test and when to involve genetics.” In the comments section at the end of the survey, 7 different participants left comments regarding their personal view on when genetic testing for OI should be ordered. Here are 4 examples of strikingly different points of view:

> “I try not to [order genetic testing] if there is no clinical evidence for OI.”
>
> “I've ordered genetic testing in every case in which there's no guilty confession.”
>
> “I never order molecular testing to rule out OI … by doing so, you have given the defense the idea that it could be a possibility. If you don't think it is OI, don't order the test.”
>
> “I think it should be tested in the majority of cases suspicious of non-accidental trauma.”

Follow up testing after VUS result

Providers were asked about the procedures carried out when a patient’s genetic test result for *COL1A1* and *COL1A2* came back as a VUS. The most common response was directed VUS testing of parents (mean score = 3.78). The other results in order from most common to least common were as follows: Second tier testing (deletion/duplication testing or biochemical analysis) (mean score= 3.09), nothing (VUS is the end result) (mean score= 2.63), a different procedure (other) (mean score= 2.57), sequencing of other genes associated with OI (mean score= 2.55), directed VUS sequencing of other family members besides the parents (mean score= 2.39), start their patient on treatment for OI (for example, medication and physical therapy) (mean score= 2.00), and lastly, having the results of the test confirmed by a second

laboratory (mean score= 1.37). One participant commented that, “Child advocacy team manages the case and informs us if more action is needed.”

As a follow up question, participants were asked who typically requests the tests that they had selected in the previous question. Physicians stated that they (themselves) were the most likely to direct the follow up. Another member of the medical team was second most likely to request the procedure, except in the case of sequencing other genes associated with OI, in which case the defense attorney is the second most likely. See Appendix 3 (Question 6, pg. 25) for complete details.

The most common reasons listed for why any follow-up procedures requested either by themselves or another stakeholder would not be carried out are listed in order from the most common reason to the least common: Financial reasons (63%), lack of access to the child (32%), family request (20%), other reasons (23%), defense attorney request (7%), legal reasons (4%), and prosecuting attorney request (2%). Despite fact that financial reasons were the most common reason listed, the majority of comments emphasized the role of the family in follow up procedures:

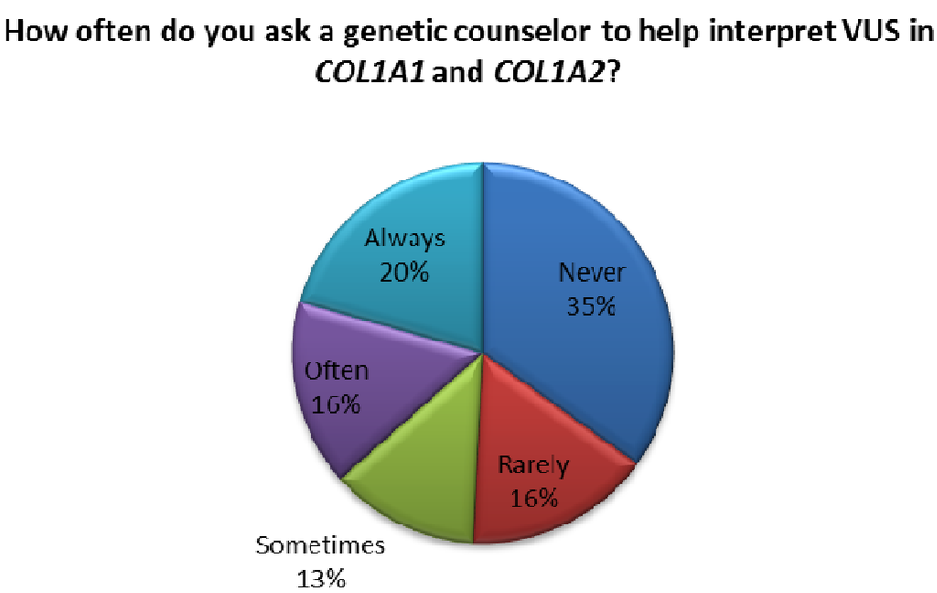
> “Families are learning NOT to have VUS tested in the parents as this puts OI likely in the suspected NAT [non-accidental trauma]”
>
> “Parent unavailable or unwilling to cooperate”
>
> “Family does not follow up with recommended parental/family testing”
>
> “Obviously, if [the child is] not with the biologic parents at this point, follow up may not get done. If [the child is] with the biologic parents, [follow up] may not get done even if recommended (I presume based on legal counsel).”

Utilization of genetic counselors

Most participants indicated that when a patient has genetic testing on the basis of OI vs. NAI and is found to have a VUS, assistance of a genetic counselor (GC) is often not utilized: 51% never or rarely seek help from a GC, 29% sometimes or often use GCs, and 20% always ask a GC for help.

The majority (86%) of those that never asked for help interpreting results indicated that as a trained geneticist they did not need help, but 5% indicated that they did not have easy access to a GC. One participant commented that as a medical geneticist, he or she answered the question to reflect how often a non-geneticist *should* ask a genetic counselor for help. One participant that self-identified as both a geneticist and a pediatrician stated "Answer to the use of a GC is predicated on having a GC in the office. My portion of the genetic practice does not have a GC generally available." Results are depicted in Figure 5.

Figure 5. Frequency with which participants ask a genetic counselor for help in interpreting VUS in *COL1A1* and *COL1A2*



Return of results

The results of the genetic test for OI are disclosed to the following stakeholders in the following order of frequency: the physician that referred the patient for genetic testing (mean score= 4.79), the parents of the child (mean score= 4.56), the social service agency representative (mean score= 3.92), the defense attorney (mean score= 3.20), the prosecuting attorney (mean score= 3.13), unknown (mean score= 1.78), and other (mean score= 1.71).

When parents or guardians receive the results, the following reactions are observed in order from most to least frequent: confusion regarding the test results (72%), emphasized by the comment, “They think that the kid has a disease that explains the fracture”, frustration (46%), relief (23%), other (20%), unknown (18%), denial (9%), guilt (2%), grief (2%). One comment in particular highlighted the complexity of the situation: “Mixed response depending on how court system views results”.

Actions taken by social or legal services

One of the questions asked participants how often patients with a question of OI versus NAI who are found to have a VUS in *COL1A1* or *COL1A2* are removed from their home without further testing. However, according to comments received by respondents, this question is difficult to answer because in most cases, children are placed into protective custody long before genetic test results for OI are returned:

> “The child's removal from the home almost always pre-dates the genetics clinic visit and any testing”
>
> “My experience has been that child is placed in foster care before VUS would return if suspicion is high enough so VUS doesn't really drive that train.”

Follow up for reclassification of VUS status

Nearly half the participants (42%) tell the family of children in which a VUS was identified that they (the family) may contact them (the physicians) to find out if their identified variant is ever reclassified as either a benign variant or pathogenic mutation. 20% say that their office will contact the patient in the event that the variant is reclassified, 6% point the family to resources to track future changes on their own, and 5% does not discuss the issue at all (Figure 7). 27% marked “Other”, with most of the comments referencing that the patient is encouraged to come back for a follow up appointment between 1 and 3 years, at which time the VUS is reassessed. Participants indicated that approximately half of their patients with a VUS in *COL1A1* or *COL1A2* return to the clinic at a later date for a reassessment of their clinical symptoms, checking in for a possible diagnosis of OI at that time. No data was collected on how many of these patients that return to the clinic are actually diagnosed with OI.

Figure 7. Frequency of methods used for keeping parents informed about changes in VUS status

Discussion

The occurrence of unexplained fractures in children is a commonly encountered clinical scenario in which providers and investigators must try to distinguish between an innate predisposition for fractures, such as OI, and non-accidental injury. The need to differentiate OI from NAI is best performed by an experienced clinician familiar with OI[34], however, assays such as biochemical and genetic tests are important complementary tools that may be necessary in some circumstances[Error! Bookmark not defined.Error! Bookmark not defined.].

One theme identified in this study is that there are differential practices and provider perspectives in both ordering genetic testing in cases of unexplained fracture(s) in a child and in the follow up procedures if a VUS is identified, despite published guidelines[Error! Bookmark not defined.Error! Bookmark not defined.]. This raises both ethical and legal concerns in regards to the inequalities between investigations, depending on where a child is evaluated. The EMQN recently (2012) published a recommended approach to diagnosing OI to help guide providers and the guidelines specifically address recommendations for VUS follow-up procedures; however, these guidelines are not universally followed. One possible explanation is that the guidelines available are issued by a European organization and this study was performed in an American population. In addition, according to this study, there are many barriers of various types that prohibit subsequent procedures from being carried out (financial reasons, lack of access to child, uncooperative family, etc.) Fortunately, these barriers are not all insurmountable; both policy changes and improvement in education can help address some of the obstacles. For example, improving the education that parents receive on the meaning of a VUS might help them understand why it is important to allow the lab to test their DNA as part of segregation analysis, or why it may be necessary to test their child for mutations in different genes than had been analyzed previously. Stakeholders involved in this policy change could include health providers,

genetic counselors, and Child Protective Services, depending on the situation. It may even be useful to consider the possibility of a multimedia approach to improving parental understanding of VUS, in light of previous research suggesting that some health care providers may not be the most adept at explaining the concept[41]. In addition, policy changes that mandate laboratories to keep an updated database on changes to VUS status may also be useful. As indicated in previously published literature, it is important for clinics to facilitate communication about VUS reclassification, either by maintaining current contact information for patients' families, or by indicating the patient's (and family's) role in requesting updates[35]. A combination of approaches requiring effort on behalf of the laboratories, the clinics, and the parents is likely the best method to ensure that all the information of importance is accessible to any and all interested parties.

Another finding of this study was that respondents differed on to whom they returned the genetic test results. Particularly surprising was that only 68% of participants commented that they always return VUS results from a genetic test for OI back to the parents of the child, and 23% said that they usually do. This raises questions about the ethics of not returning results to parents, more than 9% of the time. The ACP Ethics Manual further indicates, "Information should be disclosed to patients and, when appropriate, family caregivers or surrogates, whenever it is considered material to the understanding of the patient's situation, possible treatments, and probable outcomes"[36]. This statement supports that parents should be informed of their child's genetic test results, regardless of whether the results hold certain clinical significance or not.

Furthermore, the ACMG published a policy statement in 2013 indicating that during diagnostic testing, parents should be engaged in the informed consent process in regards to genetic testing[37]. Unfortunately, when a family unit is disrupted due to social services or legal mandate, the parents may not even be told that genetic testing is being done. Evidence of the lack of interaction between provider and family was supported by a number of comments left by

respondents from this survey stating for at least part of the time they were handling the case, they were denied access to either the child or one or both of the parents. If a family unit is disrupted, either appropriately or inappropriately, it makes it difficult if not impossible for providers to communicate important information with families, request more follow up tests that may be informative (parental DNA is often requested for segregation analysis), and it hinders the ability of family members to ask questions of the providers. This is evidence that intervention from the legal system and social circumstance can impact the standard of care for a child.

The above findings are similar to other studies of VUS result return in other groups. In one study from Australia, general health professionals (GHPs) were asked about their preferences for informing parents about VUS results and variants of certain clinical significance for chromosomal microarray (CMA) technology. It was found that GHPs prefer to inform parents of a VUS 88% of the time, while parents were slightly less sure about their desire to be informed of VUS, with only 64% responding that they would certainly like to know[38]. This may be due to poor understanding of the VUS result- studies in cancer genetics have shown that comprehension of variants is lowest among those receiving VUS[39, 40], and another study has shown that health care providers may have difficulty explaining VUS to patients[41].

This survey also uncovered differences among providers on whether and how to keep parents informed of any changes to a VUS status. According to respondents in this study, there is no consensus on whether the responsibility lies with the patient, the provider, the laboratory, or a combination of the three. This particular issue is partially addressed in the Dutch Society of Clinical Genetic Laboratory Specialists (VKGL) practice guidelines. According to the recommendations, “it is ***essential*** that laboratories issue an updated clinical report as new information becomes available to them (reports should be re-issued when a UV (Unclassified Variant, essentially a VUS) becomes clearly pathogenic or is not pathogenic anymore). They

remind readers that a UV report reflects “the best interpretation of the data at the time of reporting and that the most appropriate interpretation of UVs may change with time”[42]. More research is needed on whether or not most laboratories are in fact issuing the recommended updates, but certainly not all of them are, raising the question of whether or not laboratories should be required to do so. In addition, this also raises the question of how an update in reclassification should be communicated to the referring provider- whether the laboratory should be responsible for contacting the provider, or whether the provider should contact the laboratory. Moreover, once the provider has obtained the relevant information, it remains unclear how that information is going to reach the patient (or the parents of the patient if the patient is pediatric).

It is also currently being debated how often these informational updates should take place. This issue of frequency can have ethical implications, because if, for example, a patient is given a VUS result that ends up being reclassified as a mutation a week after the original diagnosis, yet the patient does not receive the information until a year later, that patient will have already lost an entire year of potential treatment or patient benefit. It is for this reason that updates to VUS status should not be delayed[43].

Because of the time urgency illustrated with the above example, and due to recommended practice guidelines published by the VKGL[42], clinical laboratories are increasingly being expected to initiate an amendment process for variant reclassification in order to maintain updated variant databases. Unfortunately, numerous problems arise in attempting to address this issue. The first is that as the number of variants increases, it will become progressively more difficult to stay up to date on each one. This is true both due to the time it would take to reanalyze each variant, as well the fact that most laboratories have no existing system to manage such updates properly. The Partners Healthcare laboratory in Massachusetts is working on initiating a new database that can manage such a task and automatically alert providers to a

change in one of their patient's variants[43], but not all labs are equipped to do so at the moment. The second problem with expecting laboratories to keep up to date variant databases is that with the way that billing works in most laboratories in the United States, there is not a way for the labs to receive reimbursement for their work in reanalysis and reclassification[43]. This may need to be adjusted at the policy level before it is reasonable to expect laboratories to comply with current recommendations.

Regrettably, even if policy changes can help solve the above problem, that only takes care of the first step in information translation. The second step is to get the information from the provider to the patient (or the patient's parents). To date, there has not been a formal statement issued on whether it is the responsibility of the patient or the provider to initiate contact, but current guidelines suggest that the best approach is a combination effort by both the provider and the patient[44].

While this split responsibility sounds like the most equitable approach, it may not be the most logical. The expectation for the provider to keep updated information on all variants that get returned to patients will become increasingly problematic as that number of variants grows. Moreover, as patients and their families move and/or switch health care providers, the ability of a clinic to recontact a patient diminishes. Because of these complications, it is not unreasonable to place the responsibility with patients to contact providers to request updates on variant status. Given that most patients have only one variant of interest, and only one provider to contact, it is logistically more sensible that each patient should be responsible for keeping themselves informed of any updates to their own variant of interest, rather than expected providers to constantly check laboratory databases and recontact each patient.

Participants in this research project primarily indicated that they ask patients to contact them in 1 to 3 years after diagnosis to check for any variant updates. While asking patients to be

responsible for checking back for updates is understandable, waiting 1-3 years may be a bit too long. As the cost of DNA sequencing goes down and the technology is getting faster, more variants are being found every day, and the information may quickly change. It would not be unreasonable to recommend that patients check back with their provider in 6 months, or a year at maximum to request available updates.

One other potential method to keep patients informed of any updates to variant status is to utilize information technology. The benefits of this are already being demonstrated by the GeneInSight database from the Partners Healthcare laboratory (mentioned above), which automatically sends out notifications to providers when one of their patient's VUS has been reclassified. It might be even more beneficial to construct an online database that would automatically alert both health providers and patients via email to any status changes to their VUS of interest, at which time the patient can then contact either their provider or a genetic counselor to request any further desired information. This proposal automates much of the work so that time and resources are not wasted.

Limitations

Selection bias**:** Contact information for participants were pulled from both the American Society of Human Genetics (ASHG) directory and from the Collagen Diagnostic Laboratory (CDL), although the majority of respondents were those pulled from the ASHG directory. This left a population group very strongly trained in genetics, which is not an accurate representation of the majority of physicians confronted with OI vs. NAI cases. It would have been preferable to include more participants from a variety of educational backgrounds, including child abuse specialists, pediatrics alone (without an emphasis in genetics), and orthopedics. This small

window of respondent's professions may also have compromised the meaningfulness of the results surrounding the use of genetic counselors.

Collection of data: It is very difficult to ask providers about how they have handled NAI vs. OI cases and summarize the data because each case is different from the next. One participant commented that genetic testing for OI vs. NAI cases is a "very complex topic with components that may not be addressed with checklists. Each case is unique." A more complete picture of the current practices and provider perspective may have been obtained through semi-structured interviews; however, the survey approach used allowed for sampling of a larger number of providers with the available resources. Participants were given the option to use text boxes for most questions, should they choose to elaborate on their response.

Additional future Research

This study focused solely on the current practices of genetic testing for OI in children with unexplained fractures and provider perspective in this realm. Future research is necessary to characterize the experience and perspective of other stakeholders that might be confronted with interpreting a genetic test result for OI, including those from social services and the legal community. One participant left a comment related to this issue, stating, "The agencies in charge of protective services are not sophisticated [regarding] genetic knowledge. The judges have difficulty understanding what a VUS is." The VKGL UV Guideline article also touches on this, saying, "Extreme caution should be taken when issuing a report of a UV to any professional who is not conversant with the complexities of such information. In these cases it is ***essential*** that careful unambiguous wording is used and it is ***essential*** to suggest discussion with a clinical geneticist." Understanding how the courts understand and act upon inconclusive genetic testing results could be helpful to identify whether gaps in knowledge exist that could be targeted

through education, with the goal of decreasing the likelihood of misappraisal of the genetic evidence.

It would also be interesting to conduct a similar study in various countries for an international comparison of how other countries handle OI vs. NAI cases. Some differences on how OI vs. NAI cases are handled internationally include the following: In Sweden, there are only about 5 children born each year with OI, so awareness of the disease is very rare. In one study, 11 out of 24 families with OI had been subject to suspicion of child abuse[45]. In Australia, where knowledge and awareness of OI is greater, children are rarely removed from their home while an investigation of suspected abuse is underway[46]. In the UK, there have been instances of clinicians refusing to take skin biopsies from children for diagnostic purposes as it could be "further abuse to an already abused child"[47]. It would be fascinating to conduct a study on provider practices and uses of VUS test results in each of these countries, and compare results to those from U.S. providers.

Conclusions

This study found that when a genetic test is returned as a VUS for a child for whom there is a question or OI or NAI, there are many differences in current practice and provider's perspective. No other group has previously investigated this question. The differences in practice raise some ethical concerns about whether or not these differences are justified, and if not, how they can be addressed. Responses from the survey helped elucidate some of the reasons for differences in both practice and perspective; this information can be used to help inform changes in policy and targeted improvement in education to eliminate some of the disparities in practice and alleviate some of the ethical concerns.

However, comments from the survey indicate that many providers agree that situations in which there is a question of OI vs. NAI are always rather difficult to address. As more is understood about OI and the genes associated with it, the diagnostic accuracy of genetic testing will likely increase which will help to allay some of the complexities of the cases. However, it is important for providers to keep in mind that even if a genetic test confirms OI, it cannot rule out NAI, as the two are not mutually exclusive.

Appendices

Appendix 1. Introduction email sent to participants

Dear Dr. _____,

You are receiving this survey because you previously referred a patient to the Collagen Diagnostic Laboratory at the University of Washington in Seattle. We are conducting a University of Washington research study. We would like to collect information regarding how physicians interpret a genetic result that comes back as a Variant of Unknown Significance (VUS) when the candidate diagnoses are Osteogenesis Imperfecta (OI) and non-accidental injury (NAI).

We will also ask a few questions regarding how you think your patients' families interpret a VUS. Your responses will help us better understand the ethical and social implications of a VUS in this specific situation (OI vs. NAI). The results of this study will help us learn what steps we can take to try to improve the accuracy of interpretations of VUS that are used in decisions related to NAI cases.

This survey should take about 5 minutes for you to fill out, and responses will be completely anonymous. Participation in the survey is voluntary, and if you choose to participate, not all questions need to be answered. No identifying information will be recorded by the Qualtrics survey software.

To complete the survey, follow the link below:

http://washington.qualtrics.com/SE/?SID=SV_7TVAWs67CFjLLfL

We greatly appreciate your time and participation in our research. If you have further questions regarding this research, feel free to contact me at eyoungb@uw.edu.

Regards,

Emily Youngblom, BA, MPHc

Institute of Public Health Genetics

Collagen Diagnostic Laboratory

Department of Pathology

University of Washington

eyoungb@uw.edu

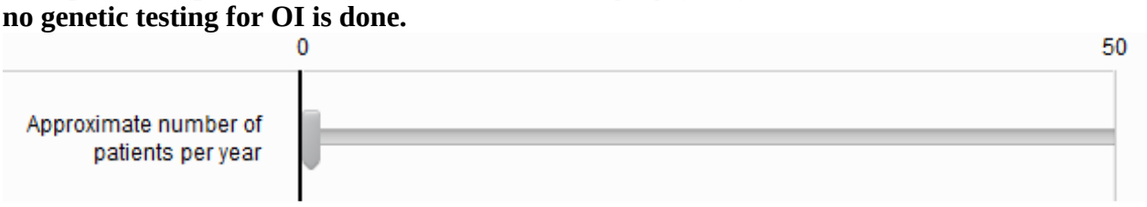
Appendix 2. Survey Questions

Interpretation of DNA sequence Variant of Unknown Significance (VUS) in infants referred for genetic testing when the diagnoses of osteogenesis imperfecta (OI) and non-accidental injury (NAI) are present

Q1 What is your specialty? SELECT ALL THAT APPLY

- ☐ Genetics
- ☐ Pediatrics
- ☐ Child abuse
- ☐ Orthopedics
- ☐ Other (please explain): _____

Q2 How often are you consulted to see patients for whom the differential diagnosis is osteogenesis imperfecta (OI) or non-accidental injury (NAI)? Please include those in which no genetic testing for OI is done.



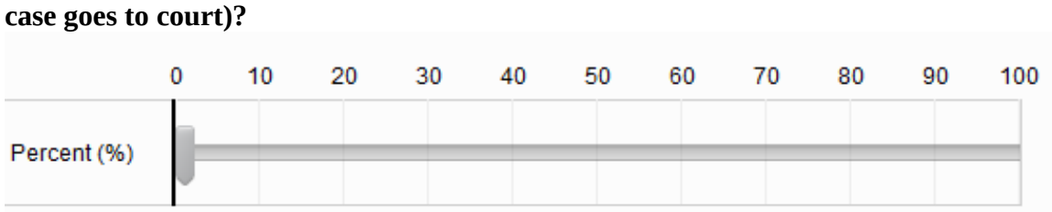
Q3 If you suspect non-accidental injury in a patient, what features help you decide whether or not to order genetic testing for OI (*COL1A1/COL1A2* genes)?

SELECT ALL THAT APPLY

- ☐ Clinical Features (blue sclera, stature, bone deformity)
- ☐ Fracture Type (multiple fractures, fractures consistent with OI)
- ☐ Absence of fractures consistent with OI
- ☐ Family History
- ☐ Social history of patient's parents (incl patient’s living arrangement, parents’ occupations, parents' criminal records, etc.)
- ☐ Court ordered/legal case (in absence of clinical features of OI)
- ☐ Parental Request
- ☐ OI testing is a protocol of my institute in all cases in which NAI is suspect
- ☐ Request by other member of care team

☐ Other (please explain): _____

Q4 What is your estimate of the percentage of your patients who are genetically tested for *COL1A1/1A2* are legal cases (child is put in foster care, charges are pressed against parents, case goes to court)?



Q5 After a patient's genetic test result for *COL1A1/1A2* comes back as a VUS, are any of the following procedures ever carried out as a next step?

	How Often?				
	Never	Rarely	Sometimes	Usually	Always
Sequence Other Genes Associated with OI	○	○	○	○	○
Directed VUS Sequencing of parents	○	○	○	○	○
Directed VUS sequencing of other family members	○	○	○	○	○
Have results confirmed by a second laboratory	○	○	○	○	○
Second tier testing (deletion/duplication testing or biochemical analysis)	○	○	○	○	○
Start patient on treatment for OI (medication, PT, etc)	○	○	○	○	○
Do nothing (end result is a variant)	○	○	○	○	○
Other	○	○	○	○	○

Q6 After a patient's genetic test result for *COL1A1/1A2* come back as a VUS, who typically recommends/requests the following procedures?

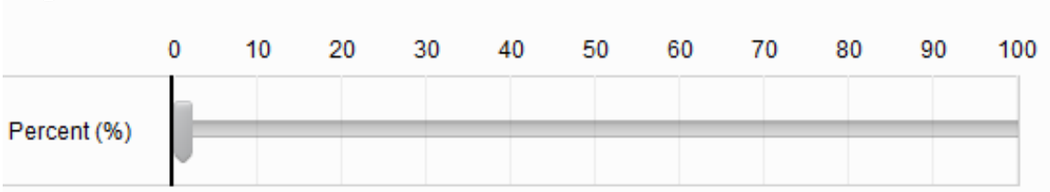
	Who typically requests this (Select all that apply)						
	Provider (You)	Family	Defense Attorney	Prosecuting Attorney	Social Worker	Other member of the medical team	N/A(never recommended)
Sequence Other Genes Associated with OI	☐	☐	☐	☐	☐	☐	☐
Directed VUS Sequencing of parents	☐	☐	☐	☐	☐	☐	☐
Directed VUS sequencing of other family members	☐	☐	☐	☐	☐	☐	☐
Have results confirmed by a second laboratory	☐	☐	☐	☐	☐	☐	☐
Second tier testing (deletion/duplication testing or biochemical analysis)	☐	☐	☐	☐	☐	☐	☐
Start patient on treatment for OI (medication, PT, etc)	☐	☐	☐	☐	☐	☐	☐
Do nothing (end result is a variant)	☐	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐	☐

Q7 If the actions from the previous question are not carried out, what is the most common reason why not?

SELECT ALL THAT APPLY

- ☐ Family request
- ☐ Defense Attorney request
- ☐ Prosecuting Attorney request
- ☐ No access to child (eg. child removed from home)
- ☐ Financial reasons
- ☐ Legal reasons
- ☐ Other (please explain): _____

Q8 Of those patients whose results come back as a VUS in *COL1A1/COL1A2*, approximately what percentage of them return to clinic for follow-up of a possible diagnosis of OI?



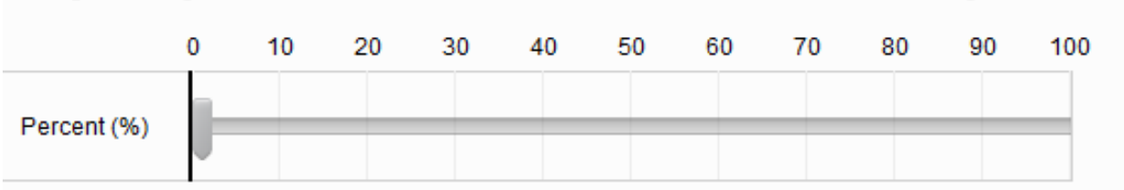
Q9 When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in *COL1A1/1A2*, what are the most frequent reactions from the parents/guardians of the patient when you return the result?
SELECT ALL THAT APPLY

- ☐ Confusion regarding test results
- ☐ Frustration
- ☐ Relief
- ☐ Guilt
- ☐ Grief
- ☐ Denial
- ☐ Unknown
- ☐ Other (please explain): _____

Q10 In your experience, to whom are the results of OI vs. NAI genetic testing typically released, and approximately how often?

	Never	Rarely	Sometimes	Often	Always
Parents	○	○	○	○	○
Physicians who referred the patient to you	○	○	○	○	○
Social service agency representative	○	○	○	○	○
Defense Attorney	○	○	○	○	○
Prosecuting Attorney	○	○	○	○	○
Unknown	○	○	○	○	○
Other	○	○	○	○	○

Q11 Of those patients whose results come back as a VUS in *COL1A1/1A2*, approximately what percentage of them are removed from their home without further testing?



Q12 When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in COL1A1/1A2, approximately what percentage of the time do you request help from a genetic counselor to interpret the results?

- Never
- Rarely
- Sometimes
- Often
- Always

(Q13 Displays if Q12 is Never)
Q13 Why not?

- I'm a geneticist
- I do not have easy access to a genetic counselor
- Other (please explain): _____

Q14 For patients who receive a VUS test result, do you discuss with the parents/guardians any plans to keep them informed of any changes to the VUS status in the future?

- Yes, I tell them my office will recontact them
- Yes, I provide resources for them to check on their own for any changes in VUS reclassification
- I tell them they can contact me
- No, I do not discuss the issue
- Other (please explain): _____

Q15 Any additional comments on genetic testing for osteogenesis imperfecta vs. non-accidental injury?

Appendix 3.

1. What is your specialty? SELECT ALL THAT APPLY

#	Answer	Response	%
1	Genetics	88	99%
2	Pediatrics	53	60%
3	Child abuse	0	0%
4	Orthopedics	0	0%
5	Other (please explain):	2	2%

2. How often are you consulted to see patients for whom the differential diagnosis is osteogenesis imperfecta (OI) or non-accidental injury (NAI)? Please include those in which no genetic testing for OI is done.

#	Answer	Min Value	Max Value	Average Value	Standard Deviation	Responses
1	Approximate number of patients per year	0.00	40.00	6.39	6.31	85

3. If you suspect non-accidental injury in a patient, what features help you decide whether or not to order genetic testing for OI (COL1A1/COL1A2 genes)? SELECT ALL THAT APPLY

Answer	Response	%
Clinical Features (blue sclera, stature, bone deformity)	66	85%
Family History	59	76%
Fracture Type (multiple fractures, fractures consistent with OI)	58	74%
Court ordered/legal case (in absence of clinical features of OI)	36	46%
Absence of fractures consistent with OI	34	44%
Request by other member of care team	28	36%
Social history of patient's parents (incl patient's living arrangement, parents' occupations, parents' criminal records, etc.)	27	35%
Parental Request	27	35%
OI testing is a protocol of my institute in all cases in which NAI is suspect	10	13%
Other (please explain):	10	13%

Other (please explain):
I order testing for OI regardless as some NAI patients may also have OI
Presence or absence of Wormian bones
continued fractures once away from perpetrator
Interview with caregivers (usually parents) to include family, pregnancy, birth and medical histories of patient to evaluate consistency with OI diagnosis
I've ordered genetic testing in every case in which there's no guilty confession

4. What is your estimate of the percentage of your patients who are genetically tested for COL1A1/1A2 are legal cases (child is put in foster care, charges are pressed against parents, case goes to court) each year?

#	Answer	Min Value	Max Value	Average Value	Standard Deviation	Responses
1	Percent (%)	0.00	100.00	36.39	33.33	74

5. After patients' genetics test result for ***COL1A1/1A2*** come back as a VUS, are any of the following procedures ever carried out as a next step? How Often?

Question	Never	Rarely	Sometimes	Usually	Always	Total Responses	Mean
Directed VUS Sequencing of parents	3	7	13	35	19	77	**3.78**
Second tier testing (deletion/duplication testing or biochemical analysis)	4	13	36	14	7	74	**3.09**
Do nothing (end result is a variant)	12	14	29	11	1	67	**2.63**
Other	4	2	4	4	0	14	**2.57**
Sequence Other Genes Associated with OI	6	27	29	6	1	69	**2.55**
Directed VUS sequencing of other family members	12	25	28	6	0	71	**2.39**
Start patient on treatment for OI (medication, PT, etc)	23	23	19	2	0	67	**2.00**
Have results confirmed by a second laboratory	48	15	5	0	0	68	**1.37**

6. After a patients' genetics test result for *COL1A1/1A2* come back as a VUS, who typically recommends/requests the following procedures? (Select all that apply)

Question	Provider (You)	Family	Defense Attorney	Prosecuting Attorney	Social Worker	Other member of the [illegible]	N/A (never recommended)	Total responses
Directed VUS Sequencing of parents	59	1	0	0	0	4	3	67
Second tier testing (deletion/duplication testing or biochemical analysis)	56	2	1	0	0	5	3	67
Do nothing (end result is a variant)	39	0	0	0	0	1	13	53
Other	6	1	0	0	1	1	6	15
Sequence Other Genes Associated with OI	46	2	4	0	0	3	8	63
Directed VUS sequencing of other family members	42	2	0	0	0	1	15	60
Start patient on treatment for OI (medication, PT, etc)	24	4	0	0	0	19	19	66
Have results confirmed by a second laboratory	7	5	1	0	0	3	42	58

7. If the actions from the previous question are not carried out, what is the most common reason why not? SELECT ALL THAT APPLY

Answer	Response	%
Financial reasons	35	63%
No access to child (eg. child removed from home)	18	32%
Other (please explain):	13	23%
Family request	11	20%
Defense Attorney request	4	7%
Prosecuting Attorney request	1	2%
Legal reasons	2	4%

Other (please explain):
low suspicion of diagnosis or abuse
Some family requests are reasonable - review in 3-6 months in non-legal case, while a request for therapy without a reasonable suspicion of a diagnosis would not be honored
Family does not follow up with recommended parental/family testing (not sure if related to legal counsel)
parent unavailable or unwilling to cooperate
no reason to test unnecessarily
Families are learning NOT to have VUS tested in the parents as this puts OI likely in the suspected NAT.
Child advocacy team manages the case and informs us if more action is needed
Family not cooperative
medical reasons (other data supports OI vs NAI)
I've never had to deal with a VUS in COL1A1/2. So I don't know what TYPICALLY happens in my state (IA). I know that if I had to deal with a VUS, I would order parental testing.
It depends on the clinical scenario rather than who is requesting other things be done. If I have a high clinical suspicion I will potentially pursue additional studies and treat as OI. If not, I will test parents and if one carries VUS and is normal I will consider as a likely benign variant.
I have never sent a test for OI without clinical indications in addition to NAT, and I have never had OI testing results return as VUS.
If the clinical suspicion for OI was weak and there is VUS only, I do nothing

8. Of those patients whose results come back as a VUS in COL1A1/COL1A2, approximately what percentage of them return to clinic for follow-up of a possible diagnosis of OI?

#	Answer	Min Value	Max Value	Average Value	Standard Deviation	Responses
1	Percent (%)	0.00	100.00	50.79	35.37	62

9. When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in COL1A1/1A2, what are the most frequent reactions from the parents/guardians of the patient when you return the result? SELECT ALL THAT APPLY

Answer	Response	%
Confusion regarding test results	47	72%
Frustration	30	46%
Relief	15	23%
Other (please explain):	13	20%
Unknown	12	18%
Denial	6	9%
Guilt	1	2%
Grief	1	2%

Other (please explain):
Depends on the indication
variable responses
mixed response depending on how court system views results
not really confused, just needing explanation and recommendations
Acceptance it is gray zone -based on clinical signs if definite clinical OI will continue to be treated as such
depends on the reason for testing to begin with.
The child advocate is in charge. The team would like to address NAT first and do limited work up for OI
They think that the kid has a disease that explains the fracture

10. In your experience, to whom are the results of OI vs. NAI genetic testing typically released, and approximately how often?

Question	Never	Rarely	Sometimes	Often	Always	Total Responses	Mean
Physicians who referred the patient to you	0	0	3	7	53	63	4.79
Parents	1	1	3	15	43	63	4.56
Social service agency representative	1	4	14	21	20	60	3.92
Defense Attorney	11	5	14	14	12	56	3.20
Prosecuting Attorney	11	5	15	14	10	55	3.13
Unknown	5	1	3	0	0	9	1.78
Other	4	1	2	0	0	7	1.71

11. Of those patients whose results come back as a VUS in COL1A1/1A2, approximately what percentage of them are removed from their home without further testing?

#	Answer	Min Value	Max Value	Average Value	Standard Deviation	Responses
1	Percent (%)	0.00	100.00	20.67	23.26	43

12. When a patient who was genetically tested on the basis of OI vs. NAI is found to have a VUS in COL1A1/1A2, approximately what percentage of the time do you request help from a genetic counselor to interpret the results?

Answer	Response	%
Never	22	35%
Rarely	10	16%
Sometimes	8	13%
Often	10	16%
Always	13	21%
Total	**63**	**100%**

12 **SKIP LOGIC Q13 unless Q12 is NEVER.**

13. Why not?

Answer	Response	%
I'm a geneticist	19	86%
I do not have easy access to a genetic counselor	1	5%
Other (please explain):	2	9%
Total	**22**	**100%**

Other (please explain):
Why is the question a gc and not a clinical geneticist or lab geneticist
I am a genetic counselor working in a team with a geneticist

13. For patients who receive a VUS test result, do you discuss with the parents/guardians any plans to keep them informed of any changes to the VUS status in the future?

Answer	Response	%
I tell them they can contact me	27	42%
Other (please explain):	17	27%
Yes, I tell them my office will recontact them	13	20%
Yes, I provide resources for them to check on their own for any changes in VUS reclassification	4	6%
No, I do not discuss the issue	3	5%
Total	**64**	**100%**

Other (please explain):
We routinely check on the status in each pregnancy
I ask the family to call our office yearly for updates
It depends on the social circumstances. If the parents have custody, they are informed that the results may get re-interpreted over time. If they elect to f/u at a 1-2 year interval, the office staff (GC/MD) re-address the VUS based on current knowledge. If the reference lab contacts this office, we contact the family as a matter of course. For a child in a state-directed custodial situation, we may lose track of the child but the record is available until the child's 25th birthdate (by law) so that the issue could be re-addressed upon re-presentation or an external records request.
I recontact!, provide resources, and urge the parents to call, follow-up. Each case is different re; response
may plan follow up visit in 1-3 years depending on age of patient
If the lab notifies us of an update, we will contact the family
we tell them to continue follow up in clinic to be updated
I continue to follow the patient
Child advocacy and genetics follows besides the PCP
encourage them to stay in touch with medical genetics
The issue is revisited on follow up and revisiting it is recommended in the consulting letter.
I never had to deal with a VUS in these genes.
I would plan routine follow up to re-evaluate the finding
I tell them they can contact me re; new information. I also inform them on existing resources that they can turn to on their own. Increasingly parents and guardians wish to have as much information as possible. they realize that it may take a long time to get a final update.
I recommend periodic follow up at which time I reassess the variant
I tell them that I will not be following up on it or contacting them about it

15. Any additional comments on genetic testing for osteogenesis imperfecta vs. non-accidental injury?
Text Response
I still think OI is basically a clinical diagnosis.
Re the previous question, I always tell patients with any VUS in any gene or microarray to re-check with us every 1-2 years. Re this question - I have no idea: Of those patients whose results come back as a VUS in COL1A1/1A2, approximately what percentage of them are removed from their home without further testing?
n/a
It is helpful, but doesn't necessarily rule out NAI. Just because a patient has OI doesn't mean that child was not abused.
I try not to do it if there is no clinical evidence for OI.
Answer to the use of a GC is predicated on having a GC in the office. My portion of the genetic practice does not have a GC generally available.
I am generally not involved in the legal aspects of these cases
If inpatient, we are rarely consulted if NAT is suspected and the ward or PICU team, or child abuse physician, is the one who initially decides to the COL1 molecular testing. The disposition of the child at discharge is based on other factors usually, not the molecular results (which may not be back). When the result is VUS, then the child is referred to genetics for further recommendations and follow up. Obviously, if not with the biologic parents at this point, follow up may not get gone. If with the biologic parents, it may not get done even if recommended (I presume based on legal counsel).
the child's removal from the home almost always pre-dates the genetics clinic visit and any testing; so it was difficult to answer the question "Of those patients whose results come back as a VUS in COL1A1/1A2, approximately what percentage of them are removed from their home without further testing?"
It is important to remember that even a child with OI can have a NAI. Our child protection team looks at the entire situation and would never base a recommendation solely on results of genetic testing, VUS or not.
I think it should be tested in the majority of cases suspicious of non-accidental trauma.
I never order molecular testing to rule out OI - I order testing is there is a suspicion that it is a possibility. COL1A1/2 testing does not fully rule out OI and by doing so, you have given the defense to idea that it could be a possibility. If you don't think it is OI, don't order the test is the mantra I go by.
yes - one of the defense attorney pointed out the statement at the end of report that says - "this test should not be used for investigational purposes and was claiming that the law suit is investigational and therefore any test result cannot be used in the court of law." I was wondering whether it can be clarified?
Would like to know the relationship between wormian bones and OI
the question about how often I turn to a genetic counselor is not valid since I am a medical geneticist so I answered with how often I thought a non-geneticist should do this
I wish the survey had introduced the question whether the care provider ever had to deal with a VUS in these genes. It is probably only a matter of time before I will deal with it, but so far we as a group of 5 geneticists have had a pretty positive experience with the CTGT lab.
I will only order studies if there are clinical findings or family history concerns, unless I am requested to do so from DHHS/lawyer ect
Usually a difficult situation

it seems that there are no guidelines as to when to test and when to involve genetics. the agencies in charge of protective services are not sophisticated re; genetic knowledge. The judges have difficulty understanding what an VUS is. No one sees the need for family studies. Again each and every case is different.
Very complex topic with components that may not be addressed with checklists. Each case is unique in terms of clinical features, degree of suspicion for OI vs. NAT, etc and those factors drive the work up and follow up. My experience has been that child is placed in foster care before VUS would return if suspicion is high enough so VUS doesn't really drive that train.
Always a difficult situation. Sometimes patients with molecularly proven OI are indeed abused by their parents. Great care must be taken in assessing the family situation.
Medical History , Family history Clinical exam findings, radiology findings still are powerful findings
We only order molecular testing in individuals who also have some additional clinical features of OI. If there is an isolated bone injury without other features, no additional testing is pursued.

[1] Marlowe A, Pepin MG, Byers PH. Testing for osteogenesis imperfecta in cases of suspected non-accidental injury. J Med Genet. 2002. 39(6):382-6. PMID: 12070242 PMCID: PMC1735162.

[2] van Dijk et al. EMQN best practice guidelines for the laboratory diagnosis of osteogenesis imperfecta. Eur J Hum Genet. 2012. 20(1):11-19.

[3] Salkeld, Luke. Family's 18 Months of Hell after Two Children Are Taken Away When Blundering Social Workers Wrongly Accuse Them of Breaking Baby's Limbs. Mail Online. http://www.dailymail.co.uk/news/article-2026555/Social-workers-wrongly-accuse-family-breaking-babys-limbs.html. Accessed 1 June 2014.

[4] We Took Our Boy to A&E with a Bump on His Head... Then We Were Banned from Being Alone with Kids for Seven Months. Mirror. http://www.mirror.co.uk/news/uk-news/we-took-our-boy-to-ae-with-a-bump-on-his-head-810869. Accessed 1 June 2014.

[5] Ravi, I., Baunthiyal, M., and Saxena, J., eds. Advances in Biotechnology. Springer India, 2014. ISBN 978-81-322-1553-0 ISBN 978-81-322-1554-7 (eBook) DOI 10.1007/978-81-322-1554-7.

[6] Salar, R.K., Gahlawat, S.K., Siwach, P., Duhan, J.S. (Eds.) Biotechnology: Prospects and Applications. Springer India, 2013. ISBN 978-81-322-1683-4. DOI 10.1007/978-81-322-1683-4_1.

[7] Jeffreys AJ, Wilson V, Thein SL, Weatherall DJ, and Ponder BA. DNA "fingerprints" and segregation analysis of multiple markers in human pedigrees. Am J Hum Genet. 1986. 39(1): 11–24. PMCID: PMC1684027.

[8] Justice For All Act of 2004. 118 STAT. 2260 PUBLIC LAW 108–405—OCT. 30, 2004. http://www.justice.gov/olp/pdf/jfaa2004.pdf. Retrieved 4 May 2014.

[9] Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: A study using the general practice research database. J Bone Miner Res. 2004. 19:1976–1981. PMID: 15537440.

[10] Spady DW, Saunders DL, Schopflocher DP, Svenson LW. Patterns of injury in children: A population-based approach. Pediatrics. 2004. 113:522–529. PMID: 14993544.

[11] Bridgman S, Wilson R. Epidemiology of femoral fractures in children in the West Midlands region of England. 1991 to 2001. J Bone Joint Surg Br. 2004. 86:1152–1157. PMID: 15568529.
[12]National Child Abuse and Neglect Data System. http://www.ndacan.cornell.edu/. Accessed 1 May 2014.
[13] Leventhal JM, Thomas SA, Rosenfield NS, Markowitz RI. Fractures in young children. Distinguishing child abuse from unintentional injuries. Am J Dis Child. 1993. 147:87–92. PMID: 8418609.
[14] Banaszkiewicz PA, Scotland TR, Myerscough EJ. Fractures in children younger than age 1 year: Importance of collaboration with child protection services. J Pediatr Orthop. 2002. 22:740–744. PMID: 12409899.
[15] Oral R, Blum KL, Johnson C. Fractures in young children: Are physicians in the emergency department and orthopedic clinics adequately screening for possible abuse? Pediatr Emerg Care. 2003. 19:148–153. PMID: 12813297.
[16] Taitz J, Moran K, O'Meara M. Long bone fractures in children under 3 years of age: Is abuse being missed in Emergency Department presentations? J Paediatr Child Health. 2004. 40:170–174. PMID: 15009543.
[17] Wardinksy TC. Genetic and congenital defect conditions that mimic child abuse. J Fam Pract 1995. 41:377-383.
[18] Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979. 16(2): 101–116. PMCID: PMC1012733.
[19] Steiner RD, Pepin M, Byers PH. Studies of collagen synthesis and structure in the differentiation of child abuse from osteogenesis imperfecta. J Pediatr. 1996. 128:542–547. PMID: 8618190.
[20] Dent JA, Paterson CR. Fractures in early childhood: Osteogenesis imperfecta or child abuse? J Pediatr Orthop. 1991. 11:184–186. PMID: 2010517.
[21] Gahagan S, Rimsza ME. Child abuse or osteogenesis imperfecta: How can we tell? Pediatrics. 1991. 88:987–992. PMID: 1945640.
[22] Genetics Home Reference, COL1A1. http://ghr.nlm.nih.gov/gene/COL1A1. Retrieved 17 November 2013.
[23] Genetics Home Reference, COL1A2. http://ghr.nlm.nih.gov/gene/COL1A2. Retrieved 17 November 2013.
[24] Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR, Lyon E, Ward BE. Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. Genet Med. 2008. 10(4):294-300. doi: 10.1097/GIM.0b013e31816b5cae. PMID: 18414213.
[25] Unpublished data. Calculated from data retrieved from the CDL database on 1 May 2014.
[26] American Bar Association, *Law Enforcement/Child Protection Cooperation,* 43. Retrieved 27 April 2014.
[27] American Bar Association, *Law Enforcement/Child Protection Cooperation,* 44. Retrieved 27 April 2014.
[28] Pence D, Wilson C. The Role of Law Enforcement in the Response to Child Abuse and Neglect. U.S. Department of Health and Human Services. 1992. https://www.childwelfare.gov/pubs/usermanuals/law/lawc.cfm. Retrieved 1 May 2014.
[29] Matter of Maria S. (Samantha S.). Justia Law. http://law.justia.com/cases/new-york/other-courts/2014/2014-ny-slip-op-50690-u.html. Accessed 1 June 2014.

[30] Johnson B, Christensen L. Educational Research: Quantitative, Qualitative, and Mixed Approaches. Online textbook. University of South Alabama. 2007.
[31] Baxter P, Jack S. Qualitative Case Study Methodology: Study Design and Implementation for Novice Researchers. The Qualitative Report. 2008. 13:4;544-559. http://www.nova.edu/ssss/QR/QR13-4/baxter.pdf. Retrieved 28 April 2014.
[32] Yin, RK. Case study research: Design and methods (3rd ed). Thousand Oaks, CA: Sage. 2003.
[33] American Society of Human Genetics (ASHG) Member Directory Search: http://www.ashg.org/pages/member_search.shtml. Accessed 15 December 2013.
[34] Tinkle BT, Wenstrup RJ. A genetic approach to fracture epidemiology in childhood. Am J Med Genet C Semin Med Genet. 2005. Nov 15;139C(1):38-54. PMID: 16278883.
[35] Murray, ML, Cerrato F, Bennett RL, Jarvik GP. Follow-up of Carriers of BRCA1 and BRCA2 Variants of Unknown Significance: Variant Reclassification and Surgical Decisions. Genetics in Medicine: Official Journal of the American College of Medical Genetics 2011. 13(12):998–1005. doi:10.1097/GIM.0b013e318226fc15.
[36] American College of Physicians. ACP Ethics Manual Sixth Edition | Medical Ethics Resource http://www.acponline.org/running_practice/ethics/manual/. Accessed 2 June 2014.
[37] Ross, LF, Saal HM, David KL, Anderson RR, American Academy of Pediatrics, and American College of Medical Genetics and Genomics. Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children. Genetics in Medicine: Official Journal of the American College of Medical Genetics. 2013. 15(3):234–45. doi:10.1038/gim.2012.176.
[38] Turbitt, E, Halliday JL, Amor DJ, Metcalfe SA. Preferences for Results from Genomic Microarrays: Comparing Parents and Health Care Providers. Clinical Genetics. 2014. doi:10.1111/cge.12398.
[39]Richter S, Haroun I, Graham TC, Eisen A, Kiss A, Warner E. Variants of unknown significance in BRCA testing: impact on risk perception, worry, prevention and counseling. Ann Oncol 2013: 24: viii69–viii74.
[40] Vos J, Gómez-García E, Oosterwijk JC, et al. Opening the psychological black box in genetic counseling. The psychological impact of DNA testing is predicted by the counselees's; perception, the medical impact by the pathogenic or uninformative BRCA1/2-result. Psychooncology. 2010: 21: 29–42.
[41] Reiff M, Ross K, Mulchandani S et al. Physicians' perspectives on the uncertainties and implications of chromosomal microarray testing of children and families. Clin Genet 2013. 83: 23–30.
[42] Bell J, Bodmer D, Sistermans E, and Ramsden S. (eds.). Practice guidelines for the Interpretation and Reporting of Unclassified Variants (UVs) in Clinical Molecular Genetics. Guidelines ratified by the UK Clinical Molecular Genetics Society (2008) and the Dutch Society of Clinical Genetic Laboratory Specialists (Vereniging Klinisch Genetische Laboratoriumspecialisten; VKGL) (2007).
[43] Aronson, SJ, Clark EH, Varugheese M, Baxter S, Babb LJ, Rehm HL. Communicating New Knowledge on Previously Reported Genetic Variants. Genetics in Medicine. 2012. 14(8):713–19. doi:10.1038/gim.2012.19.
[44] Hirschhorn K, Fleisher LD, Godmilow L, et al. Duty to re-contact. Genet Med 1999. 1:171–172.
[45] Brodin, J and Kristina M. The Preschool Children with Osteogenesis Imperfecta- Interviews with Parents. Handicap Research Group Report No. 5. 1990. http://files.eric.ed.gov/fulltext/ED331196.pdf. Accessed 1 June 2014.

[46] Flood, M. The Myth of False Accusations of Child Abuse. Women Against Violence. 2005. 16:41-43.
[47] Bishop, N, Sprigg, A, Dalton A. Unexplained Fractures in Infancy: Looking for Fragile Bones. Archives of Disease in Childhood. 2007. 92(3)3:251–56. doi:10.1136/adc.2006.106120.