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The Duty to Re-Contact for Newly Appreciated Risk Factors: Fragile X Premutation

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INTRODUCTION

The most common *heritable* form of mental retardation is fragile X syndrome (FXS), which causes 2 to 5 percent of mental retardation in males[1] and 30 to 40 percent of all cases of X-linked mental retardation.[2] FXS is caused by a change or mutation in a gene on the X chromosome, the *FMR1* (fragile X mental retardation 1) gene.[3] The gene appears in three forms, which are defined by the number of times it is repeated in a pattern of DNA, called "CGG repeats."[4] In the normal population, the number of CGG repeats varies between seven and 55; the most common number is 30. From one generation to the next, CGG repeats in the "normal" range will be transmitted stably, with no variation. Persons who have repeats of CGG in the range of 55 to about 200 are considered to have a *premutation:* while they do not exhibit FXS, the number of repeats may be unstable during passage through female oocyte production (the creation of an ovum.) Passage through male spermatocyte production is stable.[5] More than 230 repeats is considered a full mutation; this causes a shut down of a region of the *FMR1* gene that would normally produce the protein FMR (*FMRP*); a lack of *FMRP* causes FXS.

Males have only one copy of the X chromosome to depend on, and so if they have full mutation of the *FMR1* gene, they will produce no *FMRP* and will develop full FXS.[6] Most females with full mutation function normally, since they have a normal copy of the *FMR1* gene on their other X chromosome. However, 30 to 50 percent of women with full mutation will have a learning disability, and some have outright mental retardation.

The risk that premutation will expand during oogenesis and result in offspring with a full mutation will vary, based on the number of CGG repeats the woman has; women who have small premutations (55 to 70 CGG repeats) have a 10 to 17 percent risk that the premutation will expand in their offspring; slightly larger repeats (70 to 90) have a 50 to 80 percent risk that the premutation will expand, and repeats greater than 90 will have a nearly 100 percent risk of expansion.[7] These figures pertain to only 50 percent of the carriers' pregnancies, because women may transmit their other (normal) X chromosome instead. Males with a premutation transmit them stably to their daughters, who in turn may transmit the gene to their children in either its premutation state (stably or further expanded) or expanded to full mutation state.

Historically, individuals found to carry FXS premutations have been informed of the reproductive risks to their progeny, but *have been told not to worry about their own health.*

FXTAS

Recent studies have suggested that there may be an association between fragile X premutation and a late-onset disorder, fragile-X-associated tremor-ataxia syndrome (FXTAS). While the mechanism for FXTAS is not yet fully delineated, one prominent group of experts on FXS has reported evidence that its cause is this premutation.[8] Signs and symptoms of the disease are said to include tremor, ataxia, and intellectual deterioration. Onset is reportedly during late middle age; pathologic changes have been seen on MRI (magnetic resonance imaging) and at autopsy.[9] Thus far, primarily males have been reported as fully symptomatic, as in the fragile X phenotype.[10] Only a few carrier females appear to show a FXTAS phenotype.[11] Laboratory models employing fruit flies[12] and mice[13] have been reported to provide supportive evidence, and are helping to explore the molecular mechanism of disease.

While they are clinically distinct conditions, FXTAS and the early stages of Huntington disease (HD) have similarities, although the latter has virtually 100 percent penetrance and carries a well-recognized poor prognosis. ("Penetrance" is the likelihood that an individual who inherits a mutation will manifest clinical evidence of its presence.) Both are late-onset degenerative genetic conditions for which pre-symptomatic testing is available. Studies of families with HD report that the revelation of test results can be complex and fraught with anxiety, particularly for those closely related to an affected individual. Some people who are presumed to be at risk want to know their status more precisely through genetic testing; others prefer not to address the issue. An individual's result has implications for other family members. Physicians are discouraged from contacting relatives of a positive HD patient without prior consent from both the patient and the relative.

FXTAS presents different problems than HD because it is not thought to have 100 percent penetrance or relatively early onset of symptoms. Its penetrance may not, however, be trivial; one study suggests that it may be in excess of 75 percent by age 80.[14] Whereas HD is well known, FXTAS is slowly working its way into the lexicon of public health. It is included in the materials available to the general public on the website of the fragile X support group, which could, in time, prove to be a premature elevation of concern among interested parties. To provide families with at least the option of knowing the risks, physicians would have to re-contact current and former patients who are known (from previous workup) to carry FXS premutations.

The received wisdom, in the form of a carefully defined protocol for presymptomatic HD testing, may be useful in considering how to disseminate information about FXTAS. Presymptomatic testing for HD has a well-defined and relatively clear meaning when a pathologic mutation is identified; the results of presymptomatic testing for FXTAS remain ill-defined and uncertain. Thus, counseling for persons at risk for FXTAS should acknowledge current limitations of knowledge about personal prognosis (although familial reproductive aspects are clearly established).

ETHICS BACKGROUND

The *duty to re-contact* is a subset of the *duty to warn;* it is the notion that there may be an ethical and/or legal obligation for physicians to re-contact patients about advances in knowledge that may be of relevance to a previously diagnosed and/or treated condition.[15] This notion is well-known; for example, if a physician learns in reading medical literature that a medication she prescribed last week has been found to precipitate adverse events in 30 percent of patients, she should seek re-contact promptly and offer to change the regimen. The question of the temporal extent of this obligation remains moot.

If the complication is sudden death, re-contact is an urgent priority. If the complication is relatively minor, the physician may feel satisfied with informing the patient at the next scheduled office visit. It will often be sufficient to establish an office practice that identifies charts of those at newly appreciated risk, so that it is broached at the next visit. Most offices will not have a computerized database to facilitate prospec-

tive identification of such charts. Regardless of the severity of the complication, it is reasonable to assume that most people will want to know about their risks.

The American College of Medical Genetics concluded that consulting geneticists should not be expected to convey new information to past consultants, but that primary care physicians hold the responsibility to maintain or renew communications with sources of specialized information.[16] Therefore, the primary care physician is also responsible for recognizing that there may be new information *and* for informing patients of the relevant changes in their prognoses and/or treatments. This has led many clinical geneticists to add a statement to that effect at the end of consultation letters.

But practicing geneticists lack consensus on this issue.[17] Sharpe helped introduce and explore the implications of expanding the notion of duty to re-contact,[18] but did not actually advocate this expansion.[19] Knoppers proposed involving the patient in the discussion of follow-up as part of the initial consultation.[20] Lebel and colleagues studied re-contact with new information about identifiable risks that were not part of the initial consultation, and found patients were unlikely to respond to an invitation for a new consultation.[21]

Bernard and colleagues advocated a duty to re-contact persons at risk for carrier status of *FMR1* mutations, once molecular testing had become available, if these persons had first been seen in the era before the availability of such testing.[22] Such a duty can exist, of course, only after the materials in question have been shown to be firmly established in the scientific literature, a condition not as yet achieved by the researchers of FXTAS. We wish to explore the ethical problems posed by new discoveries such as this proposed clinical entity, in part to prepare the way for applying the existing notion of duty to re-contact to new situations.

PROBLEMS: BENEFICENCE, AUTONOMY

Individuals found to carry the premutation, after learning of their family history, were originally counseled that the finding had no personal clinical impact. They were informed of the risk of expansion in their offspring, but told their own health was not jeopardized. Re-contacting these individuals to inform them of the discovery of FXTAS seems, *prima facie,* to be the ethical thing to do.

However, with substantially less than 100 percent penetrance for FXTAS, as already noted, re-contact may cause unnecessary stress and anxiety for those who may never express the trait. They may spend the rest of their lives preparing for an illness that never materializes; the added psychological stress may in itself aggravate other latent stress-affected conditions. Consequently, we think that dissemination to the general public of an alert for this entity should be avoided.

Some persons may perceive re-contact as an invasion of privacy and autonomy if they do not wish to know about such risks, to avoid fear of developing symptoms. In genetics consulting, it is well-established that persons have a *right not to know* about factors that may predispose them to unpleasant future developments.[23] This is observed in some of those who seek consultation regarding HD or familial carcinoma, but who elect not to follow-up with laboratory testing, and also in those who choose not to utilize medically indicated genetic testing during pregnancy.

In simply opening the conversation by re-contact, we may reveal a possibility of a matter for concern. Conversely, failure to contact these people could be interpreted as a breach of the duty to re-contact with important new information. They may have implied consent to re-contact with new information, given the fact that they elected to be tested, although they may not have been clearly aware of the possibility of premutation status (if they were part of an extended family analysis after diagnosis of an affected relative). This is notwithstanding the complex psychosocial aspects of knowing one's carrier status.[24]

PROBLEMS: TECHNICAL

The infrastructure of a clinical genetics practice may not support a labor-intensive search for persons that we might wish to re-contact, given technologic advances. Lebel and colleagues searched a computerized database into which were entered, at the time of initial consultation, all of the family history health problems identified in a four-generation family history for some 3,000 consultants.[25] Most had been seen for either

prenatal or pediatric questions, but the database included such items as the occurrence of cancers in their first-, second-, and third-degree relatives on both sides of the family.

A couple being seen for consultation because their newborn had Down syndrome, or because of abnormal maternal serum screen results during pregnancy, or because of a history of recurrent miscarriages, would have information recorded that might include the death of a grandfather with stroke, the illness of a cousin with multiple sclerosis, or loss of two paternal aunts with breast cancer.

Contacting such people five to 10 years later (to advise them of the development of predisposition testing to identify persons at risk for breast, ovarian, and colon cancer) proved to be unwieldy, and ultimately futile. Half of those identified as potential beneficiaries from such new information could not be found for re-contact, even when the original referring physician was asked for updated telephone and address information. Not one of those contacted followed through with a consultation.

A complete report is being prepared for publication,[26] but, in summary, it is evident that the doubts expressed by Hunter and colleagues seem to be well founded when the topic for re-contact is not the same topic that drove the initial consultation.[27] If re-contact is for *the same reason* as addressed in the initial consultation, and existing databases make re-contact reasonably easy to accomplish, and the material is of potentially grave concern, then re-contact may in fact be highly useful and appropriate. When and if fragile X premutation carrier status will meet these three criteria remains to be seen.

PROBLEMS: LEGAL

Most patients previously tested for fragile X carrier status were not tested because of concern for FXTAS (an entity only recently delineated, and unknown to anyone when most of the samples were obtained). The purpose of the testing was clinical: to generate information about mutation or premutation carrier status, and to guide further testing in the family. It was not diagnostic or therapeutic. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 states that any "protected health information," including genetic information, must not be disclosed without the specific authorization by the individual.[28]

Does this mean that an individual's *own* genetic information may not be used to inform *him or her* of a possible, newly appreciated health risk without expressed consent? We doubt that this was the intent of the legislation, and think that this information may, and indeed should, be so used. FXTAS should be brought to a patient's awareness only by a primary care physician. We submit that it is appropriate for the reference laboratory, when there is knowledge of FXTAS, to find ways to alert primary care physicians of its potential importance. This opinion rests simply on the following: (1) the information already exists in others' hands, (2) it is relevant to the health of the person who was tested, and (3) the person tested has a right to be warned of the possible health hazards involved.

THE POPULATIONS

Overlapping but distinct problems arise in the ethical analysis for the three populations who must be considered in light of emerging information about newly appreciated significance of *FMR1* premutations.

1. Persons previously shown to carry FMR1 premutations. They are numerous. They often are relatives of individuals who presented clinically with FXS, but who were/are asymptomatic themselves. The effort to identify the incidence of movement disorder in this population has only begun. Some of the major laboratories have databases that may be able to identify these people easily and prospectively.

2. Persons previously identified as at-risk for carrier status who declined to be studied at first contact. These people may wish to reconsider investigating carrier status if they are advised of the new potential significance of being a carrier. They may have declined at the first contact because they did not plan to have children, and so considered the question to be theoretical and uninteresting. But now this information pertains not only to children, but to their own health. These are people who will be difficult to locate, since they elected not to enter the database. Some of them, if contacted, may still elect not to pursue the issue.

3. Persons with movement disorders of uncertain etiology whose previous workups did not include this test. If the movement disorder in this group is similar to, or at least sometimes overlaps with the features of HD and/or Parkinson disease (PD), and/or cerebellar ataxia (CA), then the laboratories that study these clinical conditions for diagnosis or presymptomatic assessment must have seen numerous samples, many of which may still be in storage, from persons whose study was unproductive of a final molecular diagnosis. Identifying the samples would not be difficult. The research under way for the genetic basis of Parkinsonism has probably produced substantial numbers of samples for which no genetic lesion has thus far been identified, but probably *FMR1* has not been investigated for these people. Certainly it is less morally ambiguous for treating physicians to re-contact these individuals, as the individuals must already recognize signs of neurologic deterioration and have begun to seek a diagnosis.

Another population not discussed here consists of families in which a new diagnosis of FXS is made, whether based on clinical assessment of an affected male, or the results of newly introduced neonatal (presymptomatic) screening. These will be families subject not to *re*-contact, but to full provision of pertinent information at the time of new diagnosis. It is clear that geneticists who approach these families for investigation must include what is known of FXTAS in the consenting process for laboratory tests that involve *FMR1* mutation and premutation status.

CONCLUSIONS

As FXTAS is being confirmed in other centers of FXS study, re-contact of populations 1 and 3 above is warranted. It is not clear, however, exactly what risk these populations should be given for the personal health implications from carrier status. Until this deficiency is met, re-contact is probably premature (at least for those in population 2). We run the risk of invading the privacy of these individuals if they prefer not to know, and we run the risk of causing them psychosocial damage if we open the possibility of insurance and/or employment discrimination on the basis of such recognition. Yet we should advise people who had an interest in the initial testing, once we know something more about the implications of their results. It may be difficult to honor their autonomy, since raising the question is a *de facto* disclosure of previously unrecognized risk. In balance, the genetics community will be derelict if we fail to make the effort if/when the specificity of this problem has been established.

As FXTAS becomes better defined and delineated, it should become standard practice to disclose the risks involved (prior to consent) to all of those tested for FXS carrier status. The uncertainty about re-contact of past patients will be clarified when the impact this information has on patients who will be forced to grapple with it prospectively is better undersood. If it is clear that knowledge about FXTAS has mental and social health implications, our expertise will increase.

One aspect of FXTAS gives physicians and ethicists a distinct advantage: time. The disorder is understood to be late in onset, and some of those at risk will never develop the phenotype at all; that proportion, and the extent to which the premutation might account for signs and symptoms interpreted as other diseases, is as yet not fully defined. Patients in the middle to late age range can be targeted first, to mitigate the initial (potentially overwhelming) breadth of the project. Patients not yet within this range have a much larger window of opportunity for re-contact. Some known premutation carriers are relatively young, as they are siblings of FXS patients, or are siblings of the children's parents, who have been diagnosed by the relatively recent practice of genetic testing.

Once a sufficient amount of information is available, how many years of files should be opened is open to question. We propose no less than five years, but no more than 10 years, on the basis of findings in a long-term re-contact study, which reports that mobility interferes with re-contact after a decade.[29] How vigorously we should seek updated contact information is another problem.

We propose that a single effort with the existing records suffices to discharge a reasonable duty. In regard to population 1, there are two approaches. Individual physicians may send a letter, or make a telephone call, to attempt re-contact. Reference laboratories may alert referring physicians to the new informa-

tion pertaining to previously ordered and reported studies. These actions should be adequate, when performed in good faith.

Population 2 does not warrant a re-contact effort since it consists of persons who, at first contact, elected not to participate, and whose contact information is presumably not available. Persons in population 1, when advised of the newly appreciated risks they face, may be encouraged to re-invite their relatives who constitute population 2. In the event that such persons re-enter the circle of discussion by asking a new question or consulting about plans for initiating pregnancy, then full disclosure regarding FXTAS (as well as FXS), obviously is obligatory.

In regard to population 3, geneticists already in contact with people who have had nondiagnostic study of genes associated with HD, PD, CA, et cetera, may re-contact them with the option to extend the laboratory effort to include *FMR1* premutations. Presumably, an appropriate provision of genetic counseling has prepared those patients for the DNA analysis that was undertaken in their work-ups thus far. Professionals should be prepared to extend genetic counseling to include implications for the patients' children and grandchildren. In work that is already under way on seeking genetic markers for Parkinson families, revisiting samples to identify *FMR1* premutations will open up an entirely different avenue of concern and discussion for those families. This is well worth the effort.

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NOTES

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