The Impact of Genetic Testing for Rett Syndrome: An Assessment of Parents’ Experiences

Master’s Thesis

Presented to

The Faculty of the Graduate School of the Arts and Sciences
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ABSTRACT

The Impact of Genetic Testing for Rett Syndrome: An Assessment of Parents’ Experiences

A thesis presented to the Genetic Counseling Program

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Rett syndrome (RTT) is an X-linked disorder diagnosed either clinically or with genetic testing. Approximately 60% of girls with RTT have had genetic testing, most born after the test’s development. In previous studies, cost, reproductive plans, confirmation of diagnosis, and learning about the condition were important factors in whether or not to pursue genetic testing, and parents decided to pursue testing to obtain a diagnosis. No studies have focused on the impact a new genetic test has on parents of children with a condition that can be diagnosed clinically. The purpose of this study was to assess the impact genetic testing for RTT has had on parents of children with RTT and to understand what factors motivated parents to obtain or forgo testing. Parents of a child with a clinical and/or genetic diagnosis of RTT participated in an anonymous, online survey with closed and open-ended questions. Most parents (91.2%) obtained genetic testing for RTT, and indicated they trust a genetic diagnosis more than a clinical
diagnosis. Parents reported testing either did not affect their family or gave them closure by confirming the clinical diagnosis. Parents most often pursued testing to confirm a diagnosis or because of physician recommendations. Parents cited the cost, test availability, and child’s age as barriers to testing. Parents of older children indicated they did not test because there is no cure for RTT and they are comfortable with the clinical diagnosis. Overall, 99.5% of parents indicated they were satisfied with their testing decision. Our results support the findings of previous studies but also suggest that the age of a child when genetic testing becomes available is an important factor in parents’ decisions to pursue testing. This study also suggests genetic testing may soon replace a clinical diagnosis of RTT.

**Keywords:** Rett syndrome; genetic testing; clinical diagnosis; genetic diagnosis; parents
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INTRODUCTION

Rett syndrome (RTT) is an X-linked genetic disorder of synapse development that affects girls almost exclusively and is the most common cause of intellectual disability in girls, second only to Down syndrome (Amir et al., 1999; Jellinger, 2003; Tropea et al., 2009). RTT occurs in 1 in 10,000 to 1 in 15,000 girls, with most cases being sporadic (Amir et al., 1999; Deidrick, Percy, Schanen, Mamounas, & Maria, 2005). RTT usually presents between six and 18 months of age, but an official diagnosis, based on the presence of a spectrum of clinical features, is often not made until the ages of two to three years (Hagberg, Aicardi, Dias, & Ramos, 1983; Jellinger, 2003).

The hallmarks of RTT are developmental regression and characteristic hand wringing movements (Hagberg et al., 1983). The clinical diagnostic criteria for RTT were originally devised in 1988 and were updated in 2001. Criteria include delayed psychomotor development, loss of purposeful hand skills between ages six months to two-and-a-half years, stereotypic hand movements such as hand wringing, impaired or failing locomotion, and social withdrawal with cognitive impairment and communication dysfunction (Hagberg, Folker, Percy, & Skjeldal, 2002; Trevathan & Moser, 1988). Interestingly, although genetic testing for RTT is available, the diagnostic criteria do not require a positive genetic test result to establish a diagnosis.

The gene responsible for most cases of RTT is the methyl-CpG-binding protein 2 gene (MECP2), which was discovered in 1999, about 16 years after RTT became recognized worldwide and started being diagnosed (Amir et al., 1999; Hunter, 2007;
In 2000, the first genetic test for RTT was developed and became available clinically. This test consisted of sequencing exons two, three, and four of the MECP2 gene; however, further research prompted the development of new versions of this genetic test to include sequencing of exon one and whole-gene deletion and duplication analysis (Deidrick et al., 2005; Weaving et al., 2005). Once this new test was developed, those girls who had originally tested negative ideally would have returned to receive the additional testing. It is unknown what proportion of these patients returned for testing, or whether they were ever contacted about the new additions to the test.

Some girls do not meet all of the diagnostic criteria for RTT, but they do meet some of the criteria and are diagnosed with an atypical variant form of RTT. Girls diagnosed with the variant forms of RTT do not always test positive for mutations in MECP2; however, two other genes have been discovered to cause RTT in some of the atypical forms: CDKL5 (Cyclin-dependent kinase-like 5) and FOXG1 (forkhead box G1) (Ariani et al., 2008; Tao et al., 2004). The development of genetic tests for these genes means that parents of children with the atypical forms of RTT can have their child re-tested with each new gene discovered. How often this happens, and the experiences parents have with these new tests, has not been ascertained.

The International Rett Syndrome Foundation (IRSF) recently published the “top five” reasons for a parent to have their child tested for a genetic cause of RTT “even if the diagnosis was made years ago” (“Top 5 Reasons”, 2009). The five reasons were to confirm a clinical diagnosis, to learn more about the disorder, to obtain information on what to expect from a specific mutation, to be eligible for clinical trials and natural history studies, and to contribute to research on MECP2 mutations. Some of these
motivations are surely important to parents of a girl with RTT, but whether they are
effective enough to motivate a parent to get testing or if they are the only reasons why parents
pursue testing is unknown.

In 2007, the North American Database for RTT was established as a registry of
girls with RTT, their mutation, what features they had, and how they were diagnosed
(Percy et al., 2007). The authors found that all clinical diagnoses were made by pediatric
neurologists, pediatricians, or geneticists and that only 60 percent of respondents had
 genetic testing performed on their child. Parents were asked to fill out a questionnaire on
whether or not they pursued genetic testing in their child, and if they had not, they were
asked for their reasons. Overall, girls born before 1990 were much less likely to have
undergone genetic testing than those born after 1990, although this difference was not
reported to be statistically significant (Percy et al., 2007; Percy & Lane, 2009). The
reason parents most often gave for not pursuing genetic testing was that they were
comfortable with their child’s clinical diagnosis and did not see a reason to pursue
additional testing or that testing was too costly. It seems that there is a divide in the ages
of girls whose parents are chose to pursue and those who chose not to pursue genetic
testing. Parents with older children may have become more comfortable with the
diagnosis by the time genetic testing was developed. Additionally, parents of older
generations may not be in contact with other RTT parents via Facebook or listservs and
therefore, they may not be influenced to pursue genetic testing by other parents as parents
in more recent generations may be. Whatever their reason, it appears that parents of older
children do not see a benefit in genetic testing at this time. It is uncertain whether any
additional breakthroughs in RTT research would motivate these parents to seek genetic test results for their daughters.

Currently, the only way to treat RTT is with symptomatic and supportive therapies (Weaving et al., 2005). However, even without a cure many girls with RTT live well into adulthood (Hunter, 2007; Kirby et al., 2010). This creates a unique situation in which parents of some girls alive today have awaited the development of both the clinical and genetic diagnosis for years, while other parents have younger children who were born into a world with both types of diagnoses for RTT (Hunter, 2007; Kirby et al., 2010). This dynamic community of parents may all have very different reactions to the development of a genetic test for RTT, and it is, therefore, important to understand the different views on genetic testing for RTT and what motivates parents to pursue this testing.

Previous studies have looked into the reasons that parents give for pursuing or not pursuing genetic testing for their child. Some reasons for pursuing testing have included identifying a cause, gathering information, obtaining a prognosis, learning recurrence risk, confirming a clinical diagnosis, and relieving feelings of guilt and isolation (Bailey, Skinner, & Sparkman, 2003; Brunger et al., 2000; Fitzgerald-Butt et al., 2010; McCarthy Veach, Truesdell, LeRoy, & Bartels, 1999; Raspberry & Skinner, 2007; Skirton, 2006a; Slack, Habecker-Green, Natowicz, & Tsipis, 1999; Uscinski, Rintell, Taylor, & Picker, 2006; Withrow et al., 2009). Parents have also stated that genetic testing and receiving a diagnosis is critical to identifying support (Bailey et al., 2003; Uscinski et al., 2006). Only one study reported that some parents did not have a personal reason to undergo
genetic testing for their child and instead went through with testing because a doctor recommended or ordered it (Withrow et al., 2009).

Despite all of the reasons to have a child tested for a gene mutation, some parents still decide not to obtain genetic testing. Therefore, it is equally important to understand why these parents do not want to obtain a genetic test result for their child. Some reasons for avoiding genetic testing include not planning to have more children, tests are too costly, and because there is no cure for the disorder (Brunger et al., 2000; McCarthy Veach et al., 1999; Skirton, Frazier, Calvin, & Cohen, 2006b). Skirton (2006a) found that some parents did not pursue genetic testing because a negative or inconclusive result would leave them with too much uncertainty. Some parents decline genetic testing because they think it is equivalent to eugenics or because they have no family history of the syndrome (Brunger et al., 2000; Skirton et al., 2006b). Therefore, it seems that many parents do not understand that “genetic” simply means “determined by genes” and is not equivalent to “familial” (Nussbaum, McInnes & Willard, 2007).

In these studies, the decision parents had to make about whether or not to pursue testing was synonymous with the decision of whether or not to obtain a diagnosis for their child. This is not the case for parents of children with RTT and other conditions diagnosed using clinical diagnostic criteria such as Neurofibromatosis I (NF1), Aicardi syndrome, or autism spectrum disorders. Children with conditions diagnosed on a clinical basis do not require genetic test results and do not “lose” a diagnosis if genetic testing is negative. Therefore, the motivations for and against pursuing optional genetic testing may be quite different for parents of children with conditions diagnosed clinically, such as RTT, than for parents with children whose diagnoses rely on genetic test results. This
difference is important for healthcare professionals to understand so they may best help these patients and their families get the support they seek.

Raspberry and Skinner (2007) took one of the first steps towards understanding why parents would want to seek a genetic test result even though they already have a clinical diagnosis. They found that parents think that a genetic test result is the “official” diagnosis for their child and that a genetic test has more “authority” than a clinical diagnosis. In fact, they found that many parents now are deciding to pursue genetic testing, because they believe that the gene is “all powerful” in a person’s health and development.

Studies have shown that in general, the public has a positive attitude toward advances in genetic technology, including genetic testing (Brunger et al., 2000; Condit, 2001; Withrow et al., 2009). Condit (2001) found that people’s moral codes and their perceived use of genetic testing influenced their attitude toward testing. Conceivably, parents of different generations may have different attitudes towards genetic testing for their child, especially if they feel the test is not necessary.

Fitzgerald-Butt et al., (2010) conducted a study on parental attitudes towards genetic testing to confirm a clinical diagnosis of hypertrophic cardiomyopathy in their child. Genetic testing has been available since 2005, but has not been pursued by many parents. They found that the parents who had undergone testing, or were willing to undergo testing soon, were generally younger in age, highly educated, aware that the disease may be genetic in origin, had knowledge of carrier testing, and knew that testing could lead to better treatment. Therefore it seems that parents who are younger and have more education are more willing to pursue genetic testing for their child as compared to
parents of older generations; however, more research is needed to confirm this hypothesis.

In order to fully understand the impact genetic testing for a syndrome diagnosed based on clinical criteria, such as RTT, has on the parents of children with these conditions, it is imperative to comprehend the experiences of many parents. Parents of children with RTT are an ideal population to study because the genetic test is relatively new and there are a significant number of parents who have chosen not to have their child tested.

To date, there have been no studies that have focused specifically on the impact a new genetic test has on parents of children with a condition diagnosed based on clinical criteria. This study attempts to assess the impact that the introduction of genetic testing for RTT has had on parents of children with this condition and to determine what factors motivate parents to obtain or not obtain genetic testing for RTT. Understanding the impact genetic testing for girls with RTT has had on their parents will help genetic counselors, medical professionals, and clinicians understand what parents of children with RTT or other clinically diagnosed conditions may go through when a test is developed for that syndrome.
METHODS

Study Design:

This was a quantitative, cross-sectional study of parents of children with RTT using an anonymous, on-line survey with both closed and open-ended questions. Quantitative analysis was conducted on the closed-ended responses and qualitative analysis was conducted on open-ended responses. This project received a status of "exempt from review" from the Brandies Committee for Protection of Human Subjects on December 10, 2010.

Sample and Recruitment:

Individuals were eligible to participate in this research study if they were the parents of a child diagnosed with RTT and over age 18 years. Only one parent was allowed to participate in this study to avoid receiving multiple responses for the same child. In an attempt to prevent both parents of a child from answering the survey, we did not allow multiple surveys from the same IP address. We did not exclude participants based on demographic characteristics such as gender, geographic location, race, or religion.

Participants were recruited through three of the International Rett syndrome Foundation’s (IRSF) media outlets: the IRSFlash e-mail newsletter, the Rettnet listserv, and the IRSF Facebook page. Therefore, participants were required to have
access to at least one of these media outlets in order to retrieve the link to the anonymous, online survey.

A committee member, who is also an International Rett syndrome Foundation staff member, posted a recruitment notice (Appendix A) on the IRSFlash listserv inviting parents to participate in the study. The post included a link to the online survey. This committee member also posted a recruitment notice (Appendix A) on the Rettnet listserv and the IRSF Facebook page with a link to the full recruitment notice available on the IRSF website that included the link to the online survey. Two reminder notices were sent out. The first was sent out three weeks after the initial posting and was posted on the IRSFlash newsletter, the Rettnet listerv, and the IRSF Facebook page. The second reminder was sent out two weeks later and was posted on the Rettnet listserv and the IRSF Facebook page. In total, the survey was available for six weeks, from December 13, 2010 to January 24, 2011.

Data Collection:

The data collection tool was an anonymous online survey (Appendix B) administered using an online survey tool (www.surveymonkey.com). The majority of the survey consisted of close-ended questions, such as, multiple-choice questions, Likert scale, and forced choice. The survey also included some open-ended questions to allow for qualitative data collection. The objective of the survey was to elucidate how the development of a genetic test for RTT has impacted parents of children diagnosed with this condition. Therefore, questions focused on parents’ initial reactions to the development of the genetic test, how they heard about the testing, whether or not they
obtained genetic testing, their reasons for their decision to obtain or not obtain genetic testing, what factors influenced this decision, how they obtained the genetic test, how they have used the results of testing, and how much they trust and value a genetic test result.

Data Analysis:

The first step of data analysis was to conduct a descriptive analysis of the parent demographics. The second step of data analysis was to assign each parent respondent to one or more of six pre-defined groups, based on their answers to three questions regarding the year their child was diagnosed, whether or not their child has been tested, and whether or not the test was positive. Once each parent respondent was assigned to their group(s), comparative analysis was conducted on the forced-choice and Likert scale questions. Quantitative data analysis was conducted using Predictive Analytic SoftWare (PASW) Statistics version 18 (also known as the Statistical Package for the Social Sciences (SPSS)). Open-ended questions were coded to identify themes using ATLAS.ti version 6.2, a qualitative data analysis software package.
RESULTS

In total, 273 parents participated in this research study. We excluded 34 data sets either because they did not meet the study criteria or because they were not completed through the half-way point of the survey. After these exclusions, 239 surveys met all study criteria and were included in the final analysis.

Participant Demographics:

Demographic information for the 239 participants included in the final analysis is presented in Table I. The majority of the respondents were mothers of children with RTT (91.2%). Most parents had only one child affected with RTT (98.7%) and this child was almost always a daughter (98.7%). Participants from different geographical areas responded in similar frequencies, with all regions of the United States and Canada represented in addition to 29 parents responding from other countries.

Most parents indicated that they had obtained genetic testing for their child (91.2%). We used a Chi-Square Independence Test to determine whether parents who had a clinical diagnosis before the genetic test was developed had obtained the genetic test in a similar frequency to the parents who received a diagnosis after the test was developed. Results indicated that there was a significant difference between these two groups of parents and whether they obtained genetic testing for their child ($\chi^2(1) = 17.153, p < .001$). The majority of parents who obtained testing were parents who had received a diagnosis of RTT after the genetic test had been developed (78.9%), while the
majority of parents who did not obtain genetic testing were parents who had received a
diagnosis prior to the development of the genetic test (61.9%).

<table>
<thead>
<tr>
<th>Table I: Demographic Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Parents</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Gender: Child with RTT</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Number of children with RTT</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>&gt; 1</td>
</tr>
<tr>
<td>Region*</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Obtained a genetic test for RTT</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Diagnosis before test available</td>
</tr>
<tr>
<td>Diagnosis after test available</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Diagnosis before test available</td>
</tr>
<tr>
<td>Diagnosis after test available</td>
</tr>
<tr>
<td>Type of diagnosis received first</td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>Genetic</td>
</tr>
<tr>
<td>Both simultaneously</td>
</tr>
<tr>
<td>Genetic cause</td>
</tr>
<tr>
<td>MECP2</td>
</tr>
<tr>
<td>CDKL5</td>
</tr>
<tr>
<td>Do not know or remember</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

* Regions: 1 = CT, MA, ME, NH, RI, VT, Prince Edward Island, Newfoundland, New Brunswick, Nova Scotia; 2 = DC, DE, MD, NJ, NY, PA, VA, WV, Québec; 3 = AL, FL, GA, KY, LA, MS, NC, SC, TN, Puerto Rico, Virgin Islands; 4 = AR, IA, IL, IN, KS, MI, MO, MN, NE, ND, OH, OK, SD, WI, Ontario; 5 = AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan; 6 = AK, CA, HI, ID, NV, OR, WA, British Columbia

Parents who had obtained genetic testing were asked whether they had received
the clinical or genetic diagnosis of RTT first. The responses were evenly divided, with
39.1% of parents indicating that they had received a clinical diagnosis first and 42.1%
indicating that they received the genetic diagnosis first. The remaining 18.8% of parents received the clinical and genetic diagnosis at the same time. Of the parents who received positive genetic test results, the majority of their children were found to have a mutation, deletion, or duplication in the \textit{MECP2} gene (94.4%).

\textbf{Table II:} Years and ages at important points in the diagnostic process.

<table>
<thead>
<tr>
<th>Year</th>
<th>Median</th>
<th>Mode</th>
<th>Mean</th>
<th>St. Dev.</th>
<th>Range</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First heard about genetic test</td>
<td>2005</td>
<td>2006</td>
<td>2004</td>
<td>3.95</td>
<td>1997 - 2010</td>
<td>239</td>
</tr>
</tbody>
</table>

| Parent age                          |        |      |      |          |             |           |
| At diagnosis                        | 33     | 35   | 33   | 6.57     | 19 - 54     | 238       |
| When first heard about genetic test | 34     | 32   | 35   | 8.03     | 19 - 62     | 238       |
| When obtained first genetic test    | 34     | 32   | 35   | 8.27     | 19 - 63     | 217       |
| At time of study                    | 41     | 36, 40, 41 | 42 | 9.79     | 22 - 69     | 238       |

| Child age                           |        |      |      |          |             |           |
| At diagnosis                        | 3      | 2    | 4    | 3.62     | 1 - 21      | 239       |
| When first heard about genetic test | 3      | 2    | 6    | 6.95     | 1 - 39      | 238       |
| When obtained first genetic test    | 3      | 2    | 6    | 7.11     | 1 - 40      | 218       |
| At time of study                    | 10     | 7    | 12   | 9.09     | 2 - 46      | 239       |

On average, parent respondents are currently in their early 40s and have affected children who are currently in their late-childhood years (Table II). Most of the children with RTT were born in the early 2000s, and most were diagnosed with RTT and had genetic testing within five years of receiving the clinical diagnosis of RTT. On average, parents were in their early to mid 30s at the time of diagnosis and when they heard about and obtained genetic testing for their child. However, the affected children varied from ages one year to 40 years at these different points in the diagnostic process.

\textit{The Impact of Genetic Testing for RTT:}

In order to assess the impact of genetic testing for RTT, we asked parents to rate their level of trust in a clinical diagnosis and a genetic diagnosis of RTT. 83.5% of parents indicated they have some degree of trust in a clinical diagnosis (Figure 1). In
contrast, almost all parents indicated that they trust a genetic diagnosis to some degree (97.4%), and most of these parents indicated that they have complete trust in the genetic diagnosis (72.4%).

Figure 1: Parents’ trust in a clinical and genetic diagnosis of RTT.

When asked to compare their level of trust in a clinical diagnosis versus a genetic diagnosis, 78.9% of parents indicated that they trust a genetic diagnosis more than a clinical diagnosis, and 18.5% of parents indicated that they trust each diagnosis equally. Similarly, 76.2% of parents indicated that they value a genetic diagnosis more than a clinical diagnosis, while 22% of parents indicated that they value each diagnosis equally.

We were interested in the potential relationship between the parents’ trust in the clinical diagnosis of RTT and the value parents placed on a genetic diagnosis. Results indicated that there was a strong negative correlation between a parent’s trust in the clinical diagnosis and the value they placed on the genetic diagnosis ($r = -.351$, $p < .001$).
In contrast, there was a modest positive correlation between parents’ trust in a genetic diagnosis and how much they value a genetic diagnosis ($r = .311, p < .001$).

Parents were also asked to indicate how important genetic testing was to them when they initially heard about it and when they obtained their first genetic test. The majority of parents indicated that genetic testing was extremely important to them at both the time when they initially heard about it (64.4%) and when they obtained the genetic test (67.4%) (Figure 2).

**Figure 2: Importance of genetic testing**

![Importance of genetic testing graph](image)

We were interested in determining whether the child’s age at various points in the diagnostic process contributed to the importance or value parents placed on genetic testing. Results indicated that there was a small negative correlation between the age of the child and the importance of testing both at the time the parents first heard about testing ($r = -.277, p < .001$) and when they obtained genetic testing ($r = -.229, p = .001$). There was also a small negative correlation between the child’s current age and the value parents placed on a genetic diagnosis ($r = -.181, p < .01$).
Parents were asked to explain how the new genetic test for RTT has affected their family. Surprisingly, the most common response was that genetic testing did not affect them: “We were indifferent since a definite diagnosis wouldn’t change her condition.” Some parents indicated that their child’s age influenced whether the genetic test would have an affect on the family: “…It’s exciting that they are making advances but my daughter is so old now that there won’t be much there to help her.” Other parents indicated that genetic testing helped them prepare for the future of their family and their affected child through obtaining better services and the option of prenatal or carrier testing for future pregnancies. One parent commented: “We decided to have more children as they could be tested in utero for the mutation.” Another parent stated: “I was able to get the exact mutation and also give a code # for diagnosis, it helped with medical tests, getting the necessary equipment.”

Parents also revealed that many different emotions came with the development of the genetic test for RTT including sadness, hope, anxiety, excitement, and closure. One parent indicated that they were sad the test had not been available sooner while other parents commented that going through the genetic testing process was like re-living their anxiety in the original search for a diagnosis: “Renewed anxiety as if we were getting the initial diagnosis once again. It didn’t change anything but it was important to us to follow through with the new opportunity to learn more than we previously knew.” Other parents expressed their excitement at the availability of a genetic test:

Very excited – while it’s vital to have a ‘name’ for your child’s illness/issues to even get into school, Retts [sic] is typically diagnosed by eliminating other diseases – a diagnosis by elimination. While I was comfortable with it, the assumption is genetic testing leaves no doubt.
Some parents indicated that the development of a genetic test gave them hope that treatments and a cure were not far behind: “The availability still held out hope for answers, possible treatment option, and the issue of my son and/or other daughter carrying the gene.” Many parents also indicated that the genetic testing provided them with a sense of closure regarding their child’s illness: “It really in finality let us know what was what. Questions that we had in our minds for years were answered.”

We also asked the parents who had a diagnosis before the testing was available and chose not to obtain testing if they would have obtained testing had it been available at the time of their child’s diagnosis. Interestingly, 11 (84.6%) of these 13 parents indicated that they would have obtained testing at the time of their child’s diagnosis. These parents explained that confirming the clinical diagnosis sooner and learning more about the syndrome earlier would have been helpful: “To verify the diagnosis. The diagnosis does not change anything. Therapies stay the same. It just lets a parent know that what their child does is consistent with the diagnose [sic] and what to expect.” Other parents described their child’s clinical diagnosis as a “process of elimination” approach in which doctors would test for everything else and if all tests came back negative, they would diagnose the child with RTT based on the clinical criteria. These parents indicated that having a genetic test available at the time of their child’s diagnosis would have helped them believe in the diagnosis and it would have helped doctors arrive at a diagnosis faster if they could test for it: “Genetic testing would have eliminated diagnosis by process of elimination. [My] daughter would not have had to undergo lots of different tests.”

Two parents indicated that they most likely would not have pursued testing if it had been available earlier because of the cost of the test, their satisfaction with the
clinical diagnosis, and the lack of a cure for RTT. One parent who was unsure of whether she would have tested earlier commented:

*If her [doctor] at the time was SURE from all the criteria that [RTT] is what she had and we had had the money to have the test done we MIGHT have considered it ‘just to be sure’, but we are glad we didn’t now[ sic] as we would have been lost if it had come back negative.*

Another parent remarked: “*[Genetic testing] would not change the outcome. She will always suffer from Rett.*”

**Factors That Contribute to the Decision of Whether to Pursue Genetic Testing:**

In addition to determining the impact that genetic testing for RTT had on parents of children affected with the disorder, we wanted to ascertain how parents decided whether or not to pursue genetic testing. Parents were asked to indicate which factors contributed to their decision to either obtain or not obtain genetic testing (Figure 3). We found that the majority of parents who did not obtain testing cited the availability of the test (76.2%) and the cost or insurance coverage of the test (71.4%) as important factors in their decision. Alternatively, we found that the ability to gain more knowledge about RTT (87.2%), confirming the clinical diagnosis (85.3%), and a doctor’s interest in having the testing performed (76.1%) were the most important factors in parents’ decisions to obtain genetic testing.

Interestingly, two factors showed a large variation in importance between the two groups of parents. Only 39.4% of parents who obtained genetic testing thought that the cost or insurance coverage of the test was an important factor in their decision, compared to 71.4% of parents who thought this was an important factor and did not obtain testing. The ability to obtain recurrence risks was an important factor to the majority of parents
who obtained testing (59.6%), but was not an important factor to the parents who did not obtain testing (33.3%). This finding is further supported by the fact that 66% of parents responded that they did not pursue genetic testing to help them decide whether or not to have more children.

**Figure 3:** Factors that contribute to a parent's decision of whether to obtain genetic testing for RTT

Parents were also asked to explain their reasons for either obtaining or not obtaining genetic testing. In both cases, parents indicated reasons similar to those analyzed statistically and most parents indicated that there were multiple reasons factoring into their decision. The three most common themes identified by parents who obtained genetic testing were confirming the clinical diagnosis, obtaining more knowledge about the condition and their child, and receiving better services for their child. The majority of parents indicated that they wanted testing to confirm the clinical diagnosis: “We wanted to know what was wrong with our daughter. We needed to have tangible answers; we wanted to see it in black and white.” Some parents wanted testing
to prove their child had RTT: “We wanted to see if she had the MECP2 mutation because she did not exhibit many clinical signs of Rett.” Others wanted testing to rule out a diagnosis of RTT: “My daughter was diagnosed with epileptic aphasia. I felt her symptoms were more than what was covered by that diagnosis. I did internet research, learned about Rett, and wanted the test mainly to disprove that it could be Rett.”

Some parents also indicated that learning more about RTT, identifying other parents as a means of support, and obtaining better care from doctors and insurance companies who doubted the clinical diagnosis were their reasons for obtaining the genetic test. One parent commented on the knowledge and support gained from the positive genetic test result:

We needed to know what we were dealing with so we could treat it, if possible. We needed to know everything about our daughter’s disabilities and medical issues so we could help her. We needed to talk to other parents who were dealing with this too for emotional support and to help us prepare for future issues.

Another parent discussed that testing was required to get their child to see a doctor specializing in RTT, “Genetic testing was needed for my daughter to take part in the Rett Clinic. Otherwise, she may not have had it since we already had her in therapy programs necessary for her specific needs.” A third parent commented that the test helped to convince doctors to treat their child for RTT:

The geneticist initially refused to test for RTT because [our daughter] didn’t show enough of the typical signs of Rett syndrome. They wanted me to wait a year to get her tested after the professor had suggested that we get the test done. We had been to specialists all over the USA and none could definitively tell me why she was losing function and so agitated. After a letter from the professor and our pediatrician the geneticist unwillingly agreed to allow the test.

Most parents who did not obtain testing cited the high cost and difficulty in finding someone to order or pay for testing as their reasons. One parent noted: “...it was difficult getting the [genetic] test because it is so expensive [and] the doctor was not
terribly familiar with Rett and didn’t want to run it.” Another parent revealed the reluctance of some doctors to diagnose or order testing for RTT without all of the clinical criteria being met:

I had read about Rett syndrome in 1997 during my constant search for a diagnosis for my daughter…I was stunned after reading about RTT as my daughter had all the markers. In a frantic call to our pediatric neurologist he was adamant that she did not have Rett syndrome due to the fact that she did not wring her hands and had purposeful hand movements, even though she [exhibited all the other signs]. During the next few years, knowing that the test was available, I asked twice more if my daughter should be tested for RTT. Our request was dismissed by two pediatric neurologists, therefore we did not pursue the testing as we believed the doctors.

Finally, some parents who had a clinical diagnosis found that insurance would not cover genetic testing: “Medicaid will not pay for genetic testing in our state unless it’s for diagnosis purposes. We have no way of justifying it since Rett syndrome has been the medical necessity given for Medicaid services for the past 12 years.”

Once we established the factors that contributed to parents’ decisions to forgo genetic testing, we were interested in knowing whether there were any factors that would make these parents reconsider their decision in the future. We found that parents were divided in their answers to this question. Out of the 21 parents who did not obtain genetic testing for their child, 8 (38%) responded that there was at least one factor that would make them reconsider their decision while another 8 (38%) responded that there was nothing that would make them reconsider their decision. The remaining 5 (24%) responded that they were unsure if there would be anything that would make them reconsider their decision.

The parents who indicated that there was something that would make them reconsider genetic testing or were unsure of whether anything would make them reconsider, were asked which factors would cause them to reconsider their decision. Most
parents (92.3%) indicated that a cure for RTT, gene therapy, or mutation-specific treatments would motivate them to reconsider their decision. A smaller number of parents (76.9%) indicated that the need to know their child’s specific mutation for an accurate prognosis or enrollment in clinical trials would make them reconsider their decision.

When parents were asked to explain any other factors that might motivate them to have their child tested most of them indicated that the cost of the test needs to be lower, insurance needs to cover it, and that doctors have to be more willing to offer and order the test. One parent answered, “Finances and better access to testing locations. We have never found anyone who would draw the blood sample for genetic testing.” Another parent commented, “Availability and doctors making it available. Also insurance needs to pick up the costs!”

One factor that was important in parents’ decision to obtain genetic testing was their doctor’s interest in testing. We ran a Chi-Square Independence Test to find out whether there were any differences in who suggested testing for children diagnosed before the test was available and those diagnosed after the test became available. Results indicated that there was a significant difference in who suggested testing for these two groups of children ($\chi^2(1) = 17.556, p < .001$). Overall, healthcare providers suggest genetic testing the majority of the time (70.6%) (Table III). However, this frequency depends somewhat on whether the child had a diagnosis before or after the genetic test was introduced. For children who were diagnosed before the genetic test was introduced, their parents (54.3%) and their healthcare providers (46.7%) suggested testing equally as often (Table III). In contrast, for children who were diagnosed after the genetic test was
developed, healthcare professionals suggested testing much more often than parents (77.3%).

Table III: Differences in who suggested testing between children diagnosed before and after the test was available.

<table>
<thead>
<tr>
<th>Suggested Testing</th>
<th>Before Genetic Test Available (%)</th>
<th>After Genetic Test Available (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>54.3</td>
<td>22.7</td>
<td>29.4</td>
</tr>
<tr>
<td>Healthcare Professional</td>
<td>45.7</td>
<td>77.3</td>
<td>70.6</td>
</tr>
<tr>
<td>Total: (n = 218)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Considering the differences in who initially suggested testing, we were interested in knowing whether there were differences in who ordered testing when it was suggested by a parent versus a healthcare professional. Results from a Chi-Square Independence Test indicated that there were significant differences in who ordered testing between these two groups ($\chi^2(6) = 18.013, p < .01$). When parents suggested testing, it was ordered by neurologists (32.8%), pediatricians (25%), and geneticists (25%) almost equally (Table IV). However, when a healthcare professional suggested testing, it was usually ordered by a neurologist (46.8%) or, less frequently, by a geneticist (28.6%).

Table IV: Comparisons between who suggested and who ordered genetic testing.

<table>
<thead>
<tr>
<th>Ordered Genetic Testing</th>
<th>Suggested Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parent (%)</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>25.0%</td>
</tr>
<tr>
<td>Geneticist</td>
<td>25.0</td>
</tr>
<tr>
<td>Neurologist</td>
<td>32.8</td>
</tr>
<tr>
<td>Developmental</td>
<td></td>
</tr>
<tr>
<td>Pediatrician</td>
<td>6.3</td>
</tr>
<tr>
<td>PCP</td>
<td>7.8</td>
</tr>
<tr>
<td>Researcher</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>1.6</td>
</tr>
<tr>
<td>Total: (n = 218)</td>
<td>100</td>
</tr>
</tbody>
</table>
Parents’ Satisfaction with Their Decision:

We asked parents who had obtained genetic testing if, knowing what they know now about genetic testing for RTT and how it has affected them, whether they would still choose to have their child tested. The vast majority of parents indicated that they would still have their child tested (99.5%). We then asked these parents to explain why they would still have their child tested for RTT and the majority of parents’ responses related to one of four themes: closure, “knowledge is power” concept, ability to obtain services, and research purposes.

Many parents indicated that genetic testing had given them a sense of closure by confirming their child’s clinical diagnosis or by relieving their feeling of guilt for their child’s illness. One parent explained that the genetic testing relieved her feelings of guilt: “[genetic testing] helped me to have a definite answer to what was going on with her and to not blame myself since this was a spontaneous mutation and nothing I or my husband had passed on to her.” Another parent described the genetic test’s ability to confirm the clinical diagnoses: “[genetic testing] helps to find the needle in the haystack rather than continue to poke at the haystack with a hit or miss philosophy.” A third parent commented, “We needed an answer/diagnosis in order to move on and enjoy our daughter, rather than be on a quest to ‘fix’ her or waste more time in search of answers.”

The second most common reason parents identified was the idea that “knowledge is power” and that knowing what is wrong with their child and what to expect is better than not knowing. One parent observed: “With knowledge there is power and with power there is hope.” Another parent remarked, “I feel like knowledge is power. When you know what you are dealing with, it helps guide you in the right direction.” Many parents
also commented on how knowing the diagnosis helps them cope with and understand their daughter’s symptoms:

*It is so much better knowing the cause of her condition then [sic] being in the dark and treating the symptoms as they arise. I only wish we could have known her diagnosis when she was 1 or 2…It truly was awful never knowing what devastating problem was coming and why.*

Two other common themes were more practical reasons to have still gone through testing: the ability to get access to special services and the idea that getting a genetic test will only help researchers understand the disorder and find a cure and it will help parents enroll their child in research studies. One parent commented, “*It is best to know exactly what one is dealing with so that you can zero in on the best information, resources, medications, doctors, and research available.*” Another parent commented on the genetic test’s usefulness to enter into research studies: “*…I suppose a genetic test doesn’t really matter as long as we know what Rett is and how to live with it. But…I tell other families to get tested so they can join the Natural History Study…*”
DISCUSSION

In this study, we explored the impact genetic testing for RTT has had on parents of children with the condition and identified the factors that were important in parents’ decisions to either obtain or not obtain genetic testing for their child. There are currently over 2,000 children affected with RTT in the world (Percy et al., 2007), and we received complete responses from 239 parents, representing about 12% of the total RTT parent population.

Participant Demographics:

Overall we had a diverse group of respondents from all regions of the United States and from other countries. The vast majority of parent respondents were mothers in their 30s and 40s. This was expected as mothers are more often the caretakers and may have been present for more of the diagnostic process. Most children were females and were the only child affected in the family, as would be expected given the inheritance pattern of RTT. Most children had a clinical diagnosis and genetic testing performed by age five years. This was not surprising, as most symptoms of RTT arise before the first two or three years of life and for most children, genetic testing was available before they turned five. Almost all children tested were found to have a mutation or deletion in MECP2, which is the gene most often mutated or deleted in RTT.
The Impact of Genetic Testing for RTT:

It appears that the genetic test for RTT may soon replace the clinical evaluation for RTT as the primary method of diagnosis. A surprising majority of parents indicated that they had received a genetic diagnosis before, or at the same time as they received a clinical diagnosis. Considering that RTT has historically been diagnosed based on clinical criteria, it is thought that most children present with symptoms, are clinically diagnosed, and then may get genetic testing to confirm this diagnosis. However, many parents indicated that their doctors wanted to do testing as soon as some symptoms arose:

*We had genetic testing done when my child was diagnosed with hypotonia when she was 12 months old. I felt it was more severe than that after months of therapies with very slow progress. At 20 months, we took her to a physiatrist, where the doctor clinically suspected [Rett syndrome] and sent for more bloodwork…*

This might indicate that the early symptoms, such as regression, are now enough to prompt doctors to order genetic testing and parents may receive the genetic test result before their child has developed all of the clinical symptoms. Alternatively, now that a genetic test is available, doctors may be wary of diagnosing a child with RTT without first confirming the diagnosis molecularly, as this parent suggests:

*When our daughter was seeing the neurologist, it took nearly 18 months [of] various genetic tests and waiting for results to get the diagnosis of Rett syndrome. The doctor would suggest a particular disorder she thought it might be, draw the blood, and sometimes we would have to wait 3 months for the results. [A]nd during those months, we would be researching whatever diagnosis she was being tested for on the internet and freaking out with what we found. When that would come back negative, we would do it all over again…[I]t would be nice if they could take one blood sample and do multiple genetic tests on it for various diagnoses so the whole process would not take so long. The doctor could say they are testing for various things but not actually give you a 'possible diagnosis’ but hopefully give the real diagnosis when it was found…*

Recently, several genetic testing laboratories have developed a genetic testing panel for RTT and Angelman syndrome because both conditions have similar clinical presentations. These panels may contribute to the trend of receiving a genetic diagnosis
first, as doctors who are unsure of which disorder a patient has could send off genetic
testing for this panel and wait for the results to diagnose the patient. If doctors do start to
rely on the genetic test for a diagnosis of RTT rather than on clinical symptoms, genetic
counselors may have to focus more time on describing what clinical symptoms to expect.
This could be the same for other conditions that are currently diagnosed by clinical
criteria. If genetic diagnoses start to replace clinical diagnoses, then counselors will have
to spend more time preparing parents for the symptoms their child is likely to develop.

While the genetic test for RTT seems to have instigated a change in the method of
diagnosis for practitioners, it has also changed parents’ views of their child’s diagnosis.
We found that most parents trust and value a genetic diagnosis more than a clinical
diagnosis. Some parents indicated that they valued a genetic diagnosis because it seems
to carry more weight with the medical professionals involved in their child’s treatment.
However, most parents explained that they value and trust a genetic diagnosis because they believe it is the “official” diagnosis. They explained that a genetic diagnosis is not
dependent on what a physician observes during a clinical evaluation; it is not subjective.
These results support the findings of Raspberry and Skinner (2007) who concluded that
parents think a genetic test has more “authority” than a clinical diagnosis. In fact, one
parent in our study echoed this idea: “I feel that genetic testing is the final authority after
receiving a clinical diagnosis. I feel that both diagnoses are important and each family
should ensure they receive both, due to false negatives/positives.”

The idea that a genetic diagnosis is the final “authority” may present difficulties
in genetic counseling sessions. Parents who believe the genetic diagnosis is the “official”
diagnosis come into the genetics clinic expecting to have testing ordered and expecting a
positive result if their child already has a clinical diagnosis. Genetic counselors need to be prepared to discuss what a negative genetic test means to parents whose child has a genetic syndrome based on clinical criteria. It will be important for counselors to stress to parents that a negative genetic test does not mean that their child does not have RTT. Genetic counselors may have to review the idea of a clinical diagnosis along with the diagnostic criteria in order to assure parents that their child does have RTT. It will be equally as important for counselors to explain that research into the causative genes of RTT and many other conditions is ongoing and that the cause of their child’s RTT may be discovered soon. These same counseling techniques may be important to employ in other cases of comparable clinically diagnosed conditions for which there is genetic testing available.

Parents of young children considered genetic testing to be more important and more valuable than parents of older children. These results support the findings of Fitzgerald-Butt et al., (2010) who concluded that younger parents are more likely to pursue genetic testing for their child than parents of older generations. In the case of RTT, we found that parents of older children may have this attitude because the genetic test does not currently have the ability to change the care or treatments for their child. Currently, there is no evidence to suggest that certain MECP2 mutations are responsible for a more severe phenotype than other MECP2 mutations and therefore, knowing the specific mutation a child has does not change the treatments or surveillance given to that child. However, in other conditions, such as Noonan syndrome, specific mutations are known to contribute to different clinical presentations, and thus, knowing a child’s specific mutation for this syndrome is important because surveillance and treatments will
be tailored to the phenotype seen with these specific mutations. Therefore, genetic testing in Noonan syndrome is important because it can affect how an affected child’s care is managed. If similar genotype-phenotype correlations were identified for RTT, then genetic testing might become more important to the parents of older children, because it could affect their child’s treatment.

Although the parents of older children did not view genetic testing as important by the time it was developed, most of them indicated that they would have had genetic testing at the time of their child’s diagnosis if it had been available then. This finding suggests that parents of older children do realize the benefits and utility of genetic testing: that it can confirm a clinical diagnosis, eradicate a diagnosis by “process of elimination”, and help parents learn more about the syndrome. However, most of these benefits become moot after living with an affected child for many years. Many of these parents indicated that genetic testing would not be helpful now because there is no cure, it is expensive, and because they are satisfied with the clinical diagnosis. These reasons were the same reasons parents gave for not pursuing genetic testing in two previous studies (Percy et al., 2007; Percy & Lane, 2009).

This is an important idea for genetic counselors and other medical professionals to keep in mind when seeing an older child with a clinical diagnosis of RTT or any clinical diagnosis for which there is a new genetic test. In the medical community, new research and developments are often considered to be good news and genetic counselors are often excited to offer a new test to a family, but it is essential to remember that some families may have an adverse reaction to these new developments. Healthcare providers should know that the parents of older children may not see the need or use in getting a genetic
test result to confirm a diagnosis that they already know their child has. In these situations, it may be important for genetic counselors to keep parents abreast of new developments in the genetics of RTT. This may involve assessing what would motivate parents to obtain genetic testing for their child or to ask parents what, if any, information they hope to obtain about their child’s condition. Understanding how these parents view the genetics of RTT will help counselors provide them with the resources and support they seek and assess what new developments may make an impact on these parents’ decisions regarding genetic testing.

Although genetic testing can evoke many different responses, most parents in this study indicated that genetic testing provided them with a sense of closure by confirming their child’s clinical diagnosis of RTT. Surprisingly, the majority of parents indicated that the new genetic test for RTT did not affect their family in any way. Many of these parents explained that the genetic test may have confirmed the clinical diagnosis, but it did not help with treatments or services for their child.

These varying reactions to the genetic test are important for genetic counselors to consider. Genetic counselors often ask parents how receiving either a positive or negative result will affect them and/or their family and what they would do with the information. In general, counselors may think that parents have not thought about the possible results of genetic testing if they answer that the results will have no affect on them. However, our research suggests that for parents with a child already diagnosed based on clinical criteria, an answer of “no affect” may be appropriate. Additionally, it will be important for counselors to discuss the fact that genetic testing may not change anything for the family. Some parents who come in expecting genetic testing to be the “absolute” answer
to their child’s issues may need to be warned that genetic testing might not provide much in the way of additional answers or help. It will be equally as important for counselors to reassure parents who have not seen much change in their family life that this is often the case for families who have a child with RTT.

**Factors That Contribute to the Decision of Whether to Pursue Genetic Testing:**

Overall, parents of children with RTT pursued genetic testing for many of the same reasons as parents of children who did not yet have a diagnosis did in previous studies. These results may indicate that the reasons parents pursue genetic testing are the same regardless of whether or not their child has a clinical diagnosis first. However, considering that 60% of the parents in our study received a genetic diagnosis before or at the same time as the clinical diagnosis, these results may be similar to previous studies because the majority of parents were pursuing genetic testing in order to obtain a diagnosis for their child. If genetic testing for RTT continues to be performed before all of the clinical symptoms arise, then most parents may come into a genetics office with similar reasons for testing: to obtain a diagnosis. As previously discussed, this would change genetic counselors roles in discussing what symptoms the parents can expect their child to develop and what a negative genetic test result might mean in the setting of a positive clinical evaluation for RTT.

Of the parents who did have a clinical diagnosis before they pursued genetic testing, the main reason they gave for pursuing testing was to confirm the clinical diagnosis. This finding supports the notion that parents consider the genetic diagnosis to be the “official” diagnosis for their child, as discussed above. Genetics professionals
should be prepared to explain the benefits and limitations of genetic testing with parents who already have a clinical diagnosis for their child. As previously discussed, it will be important that parents understand that genetic testing may not provide them with a “confirmed” diagnosis for their child. Genetic counselors should discuss the possibility of a negative genetic test with these parents and how that might affect them. Many parents who pursued genetic testing in order to obtain a diagnosis cited the ability to learn more about the syndrome, identify support groups, and obtain better services as their reasons for doing so, which were similar to the reasons cited by the IRSF (“Top 5 Reasons”, 2009). If parents who already have a clinical diagnosis pursue genetic testing for “confirmation” and their child comes back negative, it will be important to reassure them that their child still has RTT and that they can still learn about the syndrome, attend support groups, and obtain services for their child.

Two factors that were important in parents’ decisions to pursue genetic testing in previous studies were not important to parents in this study. Previous studies found that many parents pursue genetic testing to learn the recurrence risk of their child’s disorder and to relieve their own feelings of guilt and isolation (Bailey et al., 2003; Uscinski et al., 2006; Withrow et al., 2009). Parents in our study indicated that the recurrence risk of RTT was not something they were considering when they pursued testing; rather, it was a benefit they received after they had a positive test result. This finding may be more reflective of the sporadic nature of RTT than representative of parents’ overall attitudes. For instance, parents who had a clinical diagnosis of RTT before genetic testing probably already knew that RTT is not usually inherited in families and, therefore, they were not worried about obtaining the recurrence risk. However, for other conditions that are
diagnosed clinically and known to be inherited, such as NF1, parents may indicate that obtaining the recurrence risk is an important factor in their decision to pursue genetic testing. Further research will be needed to confirm this hypothesis.

Another caveat to this result is that the symptoms of RTT develop early in life, and many parents may not have been ready to think about having other children at the time when they had to decide whether or not to pursue genetic testing for their affected child. For conditions where symptoms arise later in life, parents may already have other children or be considering having additional children at the time they are presented with the option of genetic testing for their affected child. In these cases, the issue of their child’s condition recurring may be much more important than it would have been a couple of years earlier. Whether or not the recurrence risk is important for parents, it should be discussed when they are offered genetic testing and also discussed at follow-up visits as their affected child gets older and they start to consider having more children. For RTT families, it seems that reviewing the recurrence risk a few years after their child’s diagnosis may be most helpful for parents.

Although previous studies have found that parents pursue genetic testing in order to relieve their own feelings of guilt and isolation, this finding was not replicated in our study. However, parents did explain that they were able to find closure once they got molecular confirmation of the disorder. Again, this finding may be specific to parents of children with RTT and may not be typical of parents who pursue genetic testing for a clinical diagnosis of a different syndrome, such as NF1. Because RTT is known to be sporadic, parents may learn that this syndrome is not usually inherited once they receive the clinical diagnosis, and therefore, they may not feel guilty that they have “passed on”
this condition to their child, or caused it in any way. Additionally, the parents and researchers involved with RTT have constructed a very strong support community, so parents with a clinical diagnosis may not have felt isolated either. For those parents who did not yet have a clinical diagnosis of RTT, they may not have had much time to feel guilty or isolated before they received the diagnosis, because their child may not have developed all of the concerning symptoms before the doctor gave them a diagnosis. In her book *Keeping Katherine*, Susan Zimmermann describes how she felt an overwhelming sense of guilt and isolation as she watched her child grow-up with undiagnosed RTT. However, Zimmermann’s daughter was not diagnosed until late childhood. According to our results, parents are now receiving the diagnosis before their child has time to develop the symptoms. Receiving the diagnosis earlier may lessen or prevent the feelings of guilt and isolation that can develop during the diagnostic process.

The factors that contributed to parents’ decisions to forgo genetic testing may be even more important to healthcare professionals than the reasons parents gave to obtain testing because most of these factors are reparable. In general, there were three factors that contributed to parents’ decisions to not pursue genetic testing: the cost and poor insurance coverage of testing, the availability of the test, and the age of the affected individual. Previous studies have reported that the cost of testing is an important factor in parents’ decisions to forgo testing (Brunger et al., 2000; McCarthy Veach et al., 1999; Skirton, Frazier, Calvin, & Cohen, 2006b), but the lack of availability of testing has not been previously reported. Therefore, it is possible that the availability of testing is a factor specific to those who have a child with an established clinical diagnosis. This may be because parents without a diagnosis for their child might go to many doctors until they
find one who is willing to order testing and give them a diagnosis. However, parents of children with a clinical diagnosis of RTT, or any other condition, already have doctors who know what their child has and how to treat their symptoms, so for these parents, it might be more difficult to convince their doctor to order genetic testing and they may accept the clinical diagnosis.

These factors indicate that parents do not forgo testing because they do not want it; they forgo testing because they cannot logistically obtain it. Genetic counselors and other healthcare professionals may be able to help parents overcome these factors and obtain genetic testing for their child. Some parents indicated that their doctor would not order the test because their child had a clinical diagnosis of RTT. Although genetic testing is not currently necessary for treatment purposes, parents have found that it helps them to get insurance coverage, learn more about the syndrome and their child, and it eases their minds and confirms their child’s condition. Therefore, it seems that parents receive many benefits from testing and genetic testing should be offered even to those individuals with a clinical diagnosis.

While there is not much that can be done to influence the cost of the test or the insurance coverage of the testing, genetic counselors could look into alternative funding for genetic testing or grants that can sometimes be given for testing. Unfortunately, most insurance companies will not cover genetic testing for an established diagnosis, because they only pay for genetic testing that is “diagnostic.” Thus, doctors may have started to order genetic testing on a child prior to giving a clinical diagnosis because they realize the testing may not be covered otherwise. It may be worthwhile for a foundation such as the IRSF to provide funds to families who would like genetic testing but cannot afford it.
As more genetic tests become available for conditions currently diagnosed clinically, it will be important for counselors to be aware that many patients may not be able to obtain a genetic test due to the cost.

Offering genetic testing to all individuals with RTT may be especially important once a cure or mutation-specific treatments become available as genetic test results may then make a difference in treatment and management of the child’s condition. We found that the majority of parents who did not pursue testing were those whose child had a clinical diagnosis before the testing was available, which is consistent with previous research (Percy et al., 2007; Percy & Lane, 2009). About half of these parents indicated that the development of a cure or mutation-specific treatments would motivate them to reconsider their decision to forgo genetic testing. However, some parents indicated that nothing would make them reconsider their decision. Perhaps some of these parents do not believe that these developments will occur during their child’s lifetime, or that their child will be too old to benefit from new treatments or a cure. It is also possible that parents have lost their child with RTT already, and, therefore, their child would not benefit from any future research. These results indicate that the development of a genetic test may not be enough to get parents to come back for testing; it may take the development of a cure or mutation-specific treatments to motivate parents to return for genetic testing. Once this happens, it will be important for genetic counselors to review with parents both genetic testing and the way in which a child’s treatment may be influenced by knowing their genetic status. This might mean that genetic counselors see the same families every few years as new developments are made in the field to keep them updated with the research in the event that some new research will only be helpful if their child has testing.
Alternatively, it may be advantageous for counselors to assess what factors, if any, would make parents of older children want to pursue genetic testing. This way, once one of these developments occurs the counselor may re-contact the family for testing, or, alternatively, the counselor will know not to contact the family again for testing if they have indicated that nothing would change their decision to forgo testing.

Many parents indicated that their doctor’s interest in genetic testing was a factor that influenced their decision to get testing, which was consistent with previous research (Withrow et al., 2009). We found that after the genetic test had been developed, healthcare professionals were suggesting testing much more often than parents were. This finding supports the idea that genetic testing is starting to replace a clinical evaluation as the primary method of diagnosing RTT, as discussed previously. In contrast, for girls diagnosed before the testing was available, the doctors may not have suggested testing because these girls had developed all the clinical signs and they did not see the need for testing, thereby leaving time for the parents to discover the genetic test and ask for it themselves. Alternatively, doctors may have known that most insurance companies would not pay for a diagnostic test to be performed if a child already has the diagnosis in question, and therefore did not suggest testing to their patients’ parents. Further research is needed to verify these hypotheses.

We also found that when parents suggested testing, it was ordered equally as often by pediatricians, geneticists, and neurologists. However, when a healthcare professional suggested testing, it was almost always ordered by either a neurologist or a geneticist. This may indicate that parents who discovered genetic testing for RTT may have suggested it to the doctor their child was due to see next. Alternatively, geneticists and
neurologists are most often the specialists who follow girls with RTT, and they may have been more aware of new developments in RTT testing and research. They may also be the doctors most concerned with establishing a molecular diagnosis to support their own clinical diagnosis.

Parents’ Satisfaction with Their Decision:

Almost all parents indicated that they were satisfied with their decision to either obtain or not obtain genetic testing for their child. This is a reassuring finding in that it suggests that most parents took the time to ensure that their decision was the best decision for themselves, their child, and their family. As genetic counselors continue to see patients with a clinical diagnosis of RTT for genetic testing, it will be important to review why the family would like to get genetic testing and to explore the family’s thoughts on what is best for them and their child. Likewise, as other disorders move from having a clinical diagnosis to having a genetic diagnosis, it will be important for genetic counselors to discuss with the family their reasons for pursuing testing and how they imagine this will affect the family and the affected child.

Study Limitations:

This study was retrospective and asked parents to recall how the genetic test affected them and their motivations for obtaining or not obtaining genetic testing. It is possible that some parents may have found it particularly difficult to separate what was important to them when they pursued genetic testing with how they have benefited from either obtaining or not obtaining the test, causing recall bias. Additionally, parents
without a previous clinical diagnosis may have exaggerated the affect that genetic testing had on their lives because this was how they received their child’s diagnosis. If more parents had received a clinical diagnosis first, we may have obtained different results. Thus, it was difficult to separate how parents felt about the genetic test from how they felt about finally having a diagnosis.

We found that most of our respondents were in their 30s or 40s with affected children in late childhood. Therefore, there may have been a response bias with the parents who had a child diagnosed within five years of the genetic test’s development being the more likely respondents. The method of recruitment may have contributed to this response bias, as all recruitment was done online through the parent listserv, IRSF e-newsletter, and Facebook page. It is possible that most parents of older children are no longer involved with the IRSF and the online RTT community and they may have missed the recruitment. It is equally likely that parents of young children who are newly diagnosed may not be active members of these online RTT communities yet. Additionally, parents who are distrustful of the medical or research community most likely did not participate in this study. It may be reasonable to assume that these parents are also those less likely to obtain the genetic test for RTT. Therefore, by the very nature of this study being research we may have missed an important part of the RTT parent population and this may explain our relatively low response rate of parents who did not obtain genetic testing.

Another limitation was the survey itself. The survey was designed and completed online. Therefore, parents who are not particularly computer savvy may not have been comfortable with taking an online survey and parents who do not have access to a
computer or the internet would not have been able to complete the survey. The study was also advertised as being a survey about parents’ experiences with genetic testing. Therefore, it is possible that some parents who had a bad experience with genetic testing or who did not obtain genetic testing for their child chose not to partake in this study.
CONCLUSION

This was the first study to focus specifically on the impact a new genetic test has on parents of children with a condition that can be diagnosed clinically. We found that parents of children who were clinically diagnosed after the test was developed were more likely to obtain genetic testing. These parents cited many reasons similar to those parents who obtain genetic testing for diagnostic purposes: confirming a diagnosis, finding closure, gathering additional information, identifying support, and obtaining better services and care. Parents who did not obtain a genetic test were more often parents whose child was diagnosed before the genetic test was introduced. These parents cited the high cost of the test, the lack of insurance coverage for testing, and the reluctance of doctors to order testing.

Parents who had younger children were also more likely to think that genetic testing was important and valuable compared to the parents who had older children. Most parents indicated that they were satisfied with whichever decision they made regarding genetic testing, but some parents who did not pursue testing indicated that they would have pursued testing had it been available earlier in their child’s life.

As technology and research move forward, it is expected that many more genetic tests will be developed for conditions currently diagnosed based on clinical criteria. Our results indicate that parents with younger children will consider this testing important and may be anxious to obtain a new genetic test for many of the reasons mentioned here and in previous studies. Parents of older children may be more hesitant to pursue genetic
testing or may be refused testing due to the cost, insurance coverage, or because no
doctor will order a test for a diagnosis already established in a patient. Moving forward, it
will be important for medical professionals to consider a patient’s age, family situation,
and financial status when offering a new genetic test for an established clinical disorder.
Additionally, health professionals may have to find new ways to explain the diagnosis of
a genetic syndrome in patients who test negative but hold a clinical diagnosis.
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Results From a National Consumer Survey. American Journal of Human Genetics

APPENDIX A:
Recruitment Notices

Advertisement

*Title/Subject Line:* Research Study Recruiting Parents of Children with Rett Syndrome.

If you are the parent of a child with Rett syndrome, then there is a research study regarding your child’s diagnosis that is seeking your participation!

Look for the link to the survey in the IRSFlash e-mail sent out on [date].

Note: If you do not receive IRSFlash e-mails, please send an e-mail to: cdelaney@brandeis.edu to have the survey information and link sent to you!

Thank you for your interest and participation!
Recruitment Notice

Title/Subject Line: Research Study Recruiting Parents of Children with Rett Syndrome.

If you are a parent of a child with Rett syndrome, you are invited to participate in a research study regarding your child’s diagnosis of Rett syndrome.

My name is Christine Delaney and I am a graduate student and researcher in genetic counseling at Brandeis University. I am conducting a research study on the impact genetic testing has had on the Rett syndrome community and what has motivated parents of children with Rett syndrome to either choose to pursue genetic testing or choose not to pursue genetic testing for their child. This research is intended to help genetic counselors understand parents’ experiences with genetic testing for their children and to inform counselors on what factors may be most important to parents’ decisions regarding testing.

All parents, regardless of whether or not they chose to obtain genetic testing, are encouraged to participate in this study. All parents must be 18 years of age or older in order to participate. Only ONE parent per child may participate in this study.

This research study is voluntary and completely anonymous. It only requires approximately 10 to 15 minutes of your time.

If you are able to participate in this study to help enable genetic counselors to understand the impact genetic testing has had on families affected by Rett syndrome as well as assist to reveal why parents choose to pursue or decline genetic testing, please access the following website anytime between [date] and [date] to complete the online survey.

www.surveymonkey.com/samplelink

Please note:
- Participation in this study is voluntary and will in no way affect your relationship with IRSF or RettNet.
- The Brandeis University IRB (Institutional Review Board), Waltham, MA, has approved this research study.

If you have any questions or comments regarding this study, please feel free to contact me by email at: cdelaney@brandeis.edu or the International Rett syndrome Foundation Family Resource Manager, Jennifer Endres, at jendres@rettsyndrome.org.

Thank you for taking the time to further research for Rett syndrome!

Sincerely,
Christine Delaney, BS
Brandeis University Genetic Counseling Program, Class of 2011
APPENDIX B:
Survey

Introduction:
Thank you for accepting the invitation to participate in this research study. The purpose of this study is to understand the impact genetic testing has had on parents of children with Rett syndrome and to determine what motivates parents to pursue or decline genetic testing for their child.

Please answer all of the questions to the best of your ability and knowledge. Please read each question carefully, as some questions ask for your initial reactions and opinions to the diagnosis of Rett syndrome and to genetic testing. To answer these questions, you should try to think back to what you knew and felt at that time.

Remember: this survey is voluntary and completely anonymous. By clicking "next" at the bottom of this page, you acknowledge that you have been informed of the goals of this research study and that you consent to participate in this study.

All parents, regardless of whether or not they chose to obtain genetic testing, are encouraged to participate in this study. All parents must be 18 years of age or older in order to participate. Only ONE parent per child may participate in this study.

This research study is VOLUNTARY and completely ANONYMOUS. It requires approximately 10 to 15 minutes of your time.

If you have any questions or if you need assistance accessing the survey please feel free to contact me or the Principal Investigator of this study, Judith Jackson, MS, CGC at: jjackson@brandeis.edu.

If you have questions about your rights as a research subject please contact the Brandeis Institutional Review Board at irb@brandeis.edu or 781 736 8133.

I sincerely appreciate your participation in this research study.

Christine Delaney, BS
Brandeis University Genetic Counseling Program, Class of 2011
cdelaney@brandeis.edu
Eligibility Questions:

1. Are you the parent of a child with Rett syndrome?
   - Yes, I am a mother *(Skip to question 3)*
   - Yes, I am a father
   - No *(Skip to “Ineligible End” section)*

2. What is your child’s mother’s current age in years?
   - Ages listed: <17, 17, 18, … 79, 80, >80

3. What is your current age in years?
   - Ages listed: <17, 17, 18, … 79, 80, >80

4. Do you have more than one child with Rett syndrome?
   - Yes *(Skip to “Ineligible End” section)*
   - No

Core Questions:

5. In what year was your child with Rett syndrome born?

6. In what year was your child diagnosed with Rett syndrome?
   *(Parents who answer a year between 2000 and 2010 will skip to question 14)*

Questions for Parents Who Received a Diagnosis Before Genetic Testing Was Available:

7. In what year did you first hear about the genetic test for Rett syndrome?

8. Please describe how you initially heard about the genetic test for Rett syndrome.
   ________________________________________________________

9. Please indicate how important genetic testing for Rett syndrome was to you when you INITIALLY HEARD ABOUT IT.
   - Extremely important
   - Important
   - Somewhat important
   - Neither important nor unimportant
   - Somewhat unimportant
   - Unimportant
   - Extremely unimportant
10. Please describe your initial reaction to the new genetic test.

___________________

11. Would you have considered genetic testing for your child if the test was available at the time of your child’s diagnosis?
   - Yes
   - No
   - I am unsure

Please explain your reasons why.

___________________

12. Please describe how the new AVAILABILITY of genetic testing for Rett syndrome affected you and your family.

___________________

13. Has your child ever had genetic testing for Rett syndrome?
   - Yes (Skip to question 18)
   - No (Skip to question 29)

Questions for Parents Who Received a Diagnosis After Genetic Testing Was Available:

14. In what year did you first hear about the genetic test for Rett syndrome?

15. Please describe how you initially heard about the genetic test for Rett syndrome.

___________________

16. Please indicate how important genetic testing for Rett syndrome was to you when you INITIALLY HEARD ABOUT IT.
   - Extremely important
   - Important
   - Somewhat important
   - Neither important nor unimportant
   - Somewhat unimportant
   - Unimportant
   - Extremely unimportant

17. Has your child ever had genetic testing for Rett syndrome?
   - Yes
   - No (Skip to question 29)
Questions for Parents Who Pursued Genetic Testing for Their Child:

18. In what year did your child have their first genetic test for Rett syndrome?

19. Who initially SUGGESTED genetic testing for your child?
   o I (the parent) requested genetic testing
   o Pediatrician
   o Geneticist
   o Neurologist
   o Other (please specify): ______________________________

20. How important was genetic testing for Rett syndrome to you when you DECIDED TO PURSUE IT?
   o Extremely important
   o Important
   o Somewhat important
   o Neither important nor unimportant
   o Somewhat unimportant
   o Unimportant
   o Extremely unimportant

21. Who ORDERED the genetic test for your child?
   o Pediatrician
   o Geneticist
   o Neurologist
   o Other (please specify): ______________________________

22. Please explain the reasons why you decided to have the genetic test for Rett syndrome done.

   __________________________________________________________
23. Please indicate how important each of the following was in your decision to pursue genetic testing for your child.
   - Cost / Insurance coverage of the test
     - Extremely important
     - Important
     - Somewhat important
     - Neither important nor unimportant
     - Somewhat unimportant
     - Unimportant
     - Extremely unimportant
   - Availability of the test
     - (same options as listed above)
   - Doctor’s interest in testing
     - (same options as listed above)
   - Recurrence risk for future children
     - (same options as listed above)
   - Confirming the clinical diagnosis
     - (same options as listed above)
   - Eligibility for clinical trials and studies
     - (same options as listed above)
   - Gaining knowledge about the genetics of Rett syndrome
     - (same options as listed above)
   - Insurance / ability to obtain coverage for services
     - (same options as listed above)

24. How many times has your child had their blood drawn for genetic testing?
   - Number of times listed: 1, 2, 3, … 8, 9, 10+

25. Sometimes many genetic tests can be done using one blood sample. Considering this information, about how many genetic tests has your child had? Note: If you are unsure, please make your best guess based on the number of times your child has had their blood drawn for genetic testing.
   - Number of times listed: 1, 2, 3, … 8, 9, 10+

26. What were the results of genetic testing in your child?
   - Positive (a genetic cause was found)
   - Negative (no genetic cause was found; testing was normal) (Skip to question 34)
   - I am unsure (Skip to question 38)
Questions for Parents Whose Child has Tested Positive for a Mutation:

27. What gene is mutated, deleted, or duplicated as the cause of your child’s Rett syndrome?
   o MECP2
   o CDKL5
   o FOXG1
   o I do not remember
   o I do not know
   o Other (please specify): ____________________

28. Did you receive a clinical or genetic diagnosis first?
   o Clinical (based on physical and behavioral symptoms)
   o Genetic (based on genetic blood test results)
   o Both simultaneously

(Skip to question 34)

Questions for Parents Who Did Not Pursue Genetic Testing for Their Child:

29. Have you ever wanted to pursue genetic testing for your child, but have not been able to obtain it?
   o Yes
   o No

   If yes, please explain the reason(s) why you wanted testing.
   ____________________

30. Please explain what influenced your decision to decline genetic testing for your child.
   __________________________________________
31. Please indicate how important each of the following was in your decision to decline genetic testing for your child.
   - Cost / Insurance coverage of the test
     - Extremely important
     - Important
     - Somewhat important
     - Neither important nor unimportant
     - Somewhat unimportant
     - Unimportant
     - Extremely unimportant
   - Availability of the test
     - (same options as listed above)
   - Doctor’s interest in testing
     - (same options as listed above)
   - Recurrence risk for future children
     - (same options as listed above)
   - Confirming the clinical diagnosis
     - (same options as listed above)
   - Eligibility for clinical trials and studies
     - (same options as listed above)
   - Gaining knowledge about the genetics of Rett syndrome
     - (same options as listed above)
   - Insurance / ability to obtain coverage for services
     - (same options as listed above)

32. Is there anything that would make you reconsider your decision to not have your child tested?
   - Yes
   - No (Skip to question 40)
   - I am unsure at this time

   If yes, please explain what would make you reconsider genetic testing for your child.

33. Please indicate which of the following would motivate you to pursue genetic testing for your child. (Choose all that apply)
   (Note: most of these options are not currently available for Rett syndrome.)
   - A cure for Rett syndrome
   - Gene therapy for Rett syndrome
   - Mutation-specific treatments
   - Mutation-specific predictions of symptoms/severity
   - Clinical trial(s) requiring genetic information for participation
   - None of these would motivate me to pursue genetic testing for my child.

(Skip to question 40)
Questions for Parents Who Pursued Genetic Testing for Their Child Regarding Genetic Test Results:

34. Please explain how the RESULTS of genetic testing have affected you and your family.

__________________________________________________________________

35. Please explain how you and your family have used the genetic information provided by the genetic test results.

__________________________________________________________________

36. Please indicate which of the following you have obtained with the results of your child’s genetic test. (Choose all that apply)
   o Treatment(s)
   o Prenatal testing of other pregnancies
   o Insurance coverage of services
   o Eligibility for specific services
   o Enrollment in the Rett syndrome Natural History Study
   o Enrollment in clinical trials
   o I have not obtained any of these

37. Knowing what you know now, if you could go back to the day you decided to have your child tested, would you choose to have your child tested?
   o Yes, I would have my child tested
   o No, I would not have my child tested

   Please explain your reasons why, or why not, in a few sentences.

__________________________________________________________________

Questions for Parents Who Pursued Genetic Testing for Their Child Regarding Previous Misdiagnoses:

38. Was Rett syndrome the first genetic condition your child was diagnosed with?
   o Yes *(Skip to question 43)*
   o No
Questions for Parents Who Pursued Genetic Testing for Their Child and had a Previous Misdiagnosis:

39. Please indicate the affect your child’s earlier misdiagnosis had on your decision to have your child tested for Rett syndrome.
   o Extreme affect
   o Affect
   o Some affect
   o No affect
   *(Skip to question 43)*

Questions for Parents Who Did Not Pursue Genetic Testing for Their Child Regarding Reproductive Plans and Previous Misdiagnoses:

40. Were you planning on having more children when your child was diagnosed with Rett syndrome?
   o Yes
   o No
   o We were unsure

41. Was Rett syndrome the first genetic condition your child was diagnosed with?
   o Yes *(Skip to question 46)*
   o No

Questions for Parents Who Did Not Pursue Genetic Testing for Their Child and had a Previous Misdiagnosis:

42. Please indicate the affect your child’s earlier misdiagnosis had on your decision to have your child tested for Rett syndrome.
   o Extreme affect
   o Affect
   o Some affect
   o No affect
   *(Skip to question 46)*

Questions for Parents Who Pursued Genetic Testing for Their Child Regarding Reproductive Plans:

43. Were you planning on having more children when your child was diagnosed with Rett syndrome?
   o Yes
   o No *(Skip to question 46)*
   o We were unsure
44. Did you pursue genetic testing to help you to decide whether or not you would have more children?
   o Yes
   o No

45. Please indicate how helpful the test results were to your decision of whether you would have more children.
   o Extremely helpful
   o Helpful
   o Somewhat helpful
   o Neither helpful nor unhelpful
   o Somewhat unhelpful
   o Unhelpful
   o Extremely unhelpful

Questions for All Parents Regarding Their Trust in Clinical and Genetic Diagnoses of Rett syndrome:

46. Please rate your level of trust in a clinical diagnosis of Rett syndrome (a diagnosis made by a doctor based on physical and behavioral symptoms observed in the clinic) and a genetic diagnosis of Rett syndrome (a diagnosis made based on genetic blood test results)
   o Clinical diagnosis (based on physical/behavioral symptoms)
     ▪ Completely trust
     ▪ Trust
     ▪ Somewhat trust
     ▪ Neither trust nor distrust
     ▪ Somewhat distrust
     ▪ Distrust
     ▪ Completely distrust
     ▪ N/A
   o Genetic diagnosis (based on genetic blood test results)
     ▪ Completely trust
     ▪ Trust
     ▪ Somewhat trust
     ▪ Neither trust nor distrust
     ▪ Somewhat distrust
     ▪ Distrust
     ▪ Completely distrust
     ▪ N/A
47. How much do you TRUST a genetic diagnosis of Rett syndrome when compared to a clinical diagnosis of Rett syndrome?
   o I trust a genetic diagnosis MUCH MORE than a clinical diagnosis.
   o I trust a genetic diagnosis MORE than a clinical diagnosis.
   o I trust a genetic diagnosis SOMEWHAT MORE than a clinical diagnosis
   o I trust a genetic diagnosis EQUALLY as much as a clinical diagnosis
   o I trust a genetic diagnosis SOMEWHAT LESS than a clinical diagnosis
   o I trust a genetic diagnosis LESS than a clinical diagnosis
   o I trust a genetic diagnosis MUCH LESS than a clinical diagnosis
   o Not applicable

**Questions for All Parents Regarding How Much They Value Clinical and Genetic Diagnoses of Rett syndrome:**

48. How much do you VALUE a genetic diagnosis of Rett syndrome as compared to a clinical diagnosis of Rett syndrome?
   o I value a genetic diagnosis MUCH MORE than a clinical diagnosis.
   o I value a genetic diagnosis MORE than a clinical diagnosis.
   o I value a genetic diagnosis SOMEWHAT MORE than a clinical diagnosis
   o I value a genetic diagnosis EQUALLY as much as a clinical diagnosis
   o I value a genetic diagnosis SOMEWHAT LESS than a clinical diagnosis
   o I value a genetic diagnosis LESS than a clinical diagnosis
   o I value a genetic diagnosis MUCH LESS than a clinical diagnosis.
   o Not applicable

49. Please discuss your personal views regarding the usefulness of genetic testing for Rett syndrome in a few sentences.

__________________________________________________________

50. If you have any remaining thoughts regarding genetic testing for Rett syndrome that you want to share, please do so in a few sentences.

__________________________________________________________
Demographic Questions:

51. What is your child’s gender?
   - Male
   - Female

52. Please indicate which region you currently live in:
   - Region 1 (CT, MA, ME, NH, RI, VT, Prince Edward Island, Newfoundland, New Brunswick, Nova Scotia)
   - Region 2 (DC, DE, MD, NJ, NY, PA, VA, WV, Québec)
   - Region 3 (AL, FL, GA, KY, LA, MS, NC, SC, TN, Puerto Rico, Virgin Islands)
   - Region 4 (AR, IA, IL, IN, KS, MI, MO, MS, NE, ND, OH, OK, SD, WI, Ontario)
   - Region 5 (AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan)
   - Region 6 (AK, CA, HI, ID, NV, OR, WA, British Columbia)
   - Other
Thank You:
Thank you very much for taking the time to participate in this research study. We sincerely appreciate you taking the time to share the story of your child’s diagnosis with Rett syndrome. By sharing your experience with, and views of genetic testing you will help healthcare professionals, particularly in the genetics specialty, understand what kind of impact the introduction of genetic testing has on the families of children with a genetic condition.

If you have questions or concerns about this study please feel free to contact me, the Principal Investigator for this study, Judith Jackson, MS, CGC (jjackson@brandeis.edu), or the International Rett Syndrome Foundation Family Resource Manager, Jennifer Endres, at: jendres@rettsyndrome.org

Christine Delaney, BS
Brandeis University Genetic Counseling Program, Class of 2011
cdelaney@brandeis.edu

END

Ineligible End:
Thank you for offering to participate in this research study. This study is specifically intended for parents over 18 years of age with one child affected by Rett syndrome. Please feel free to contact me or the Principal Investigator of this study, Judith Jackson, MS, CGC (jjackson@brandeis.edu) with any additional questions regarding your participation in this study.

Christine Delaney, BS
Brandeis University Genetic Counseling Program, Class of 2011
cdelaney@brandeis.edu

END
APPENDIX C
Additional Open Responses

In this appendix, we have included more of the open response answers from parents in order to convey their stories.

How parents initially heard about the genetic test:

The genetic marker was found shortly before our daughter was evaluated at Johns Hopkins. The research confirming the discovery came out just weeks after that. Because I was pregnant again, it was very important to us to test for Rett. She was found to be + for R106W. We were then able to have genetic testing performed on the amniotic sample for our unborn child, which was negative for any of the (then) known RTT mutations. She is now a healthy 10 year old. I remember having to wait for the diagnostic test to be available, all previous testing was of the research type. I think she was one of the first, if not the first to be tested outside of research labs.

When my daughter was diagnosed with Rett syndrome, it was all based on the manifestations a Rett girl would have which was seen by our pediatric neurologist—non purposeful hand movements, hyperventilates, can't walk, can't talk, seizures, etc. There is no genetic test for Rett in our country. It wasn't that important to us since we were told that it will only confirm if she really has RS and is not a CURE which is more important. Though she had [the] Genetic test in 2009 when we visited the U.S.

I heard about the test during my internet research. I was googling various topics trying to determine what an appropriate diagnosis would be for someone with my daughter's symptoms. I felt she was misdiagnosed and as it turns out I was correct. When I read about Rett I learned of the genetic test.

Our daughter was [a researcher's] first Rett patient, so the day that [the researchers] announced that [they] had found the gene that causes Rett Syndrome, [the researcher] took us to the lab and had [our daughter] tested for the mutation.

Parents initial reaction to the genetic test for RTT:

Actually, I remember being so happy that we got a positive result back. How ironic is that? No more mystery diagnosis. We had a concrete answer, and were able to test our unborn child to make sure she was not affected.

Wonderful! Jubilation! Wish it had come sooner.

Maybe the test would show that she DIDN'T have Rett Syndrome
Not very excited because I knew it could lead to abortions.

Not sure. My child had so many different tests since the age of 14 months and I got no results that I had much skepticism.

**Reasons parents would or would not have tested at the time of their child’s diagnosis if the test had been available:**

Absolutely! [sic] We had to use "process of elimination" which took quite a while.

Twelve years and 2 prior diagnoses was this the right diagnosis this time, I wanted proof. But in hindsight, I am glad she was not tested until she was 21 because we never stopped trying all kinds of therapies and she received a high school education with no one truly knowing whether she had Retts [sic] and whether that would impact her ability to learn and educators saying she couldn't do this or that because it would make no difference. In my case not having genetic testing was a blessing then.

We knew she had Rett Syndrome by her symptoms and parent's intuition. Why do ANOTHER medical procedure?

I felt satisfied with the diagnosis based on my daughter's history and recent behavior.

**Parents’ reasons for pursuing genetic testing:**

Just to confirm what we knew. We didn't worry it was familial--our older girl is 10 years older than our daughter with [R]ett, and she was better than fine--brilliant, in fact. We knew [R]ett was a fluke. And we were pretty old, so we weren't planning on more kids. We just wanted confirmation.

We really did not have any idea that she was included in this experiment. But, [we] were thrilled to get the call. She is a Rett Pioneer!

We put it off for a while, because it seemed as though the disorders they were testing for were completely devastating, and since there were no treatments or cures we didn't want to know if they had either one (Angelman or Rett). [Our daughter's doctor] explained that knowing for sure could possibly be helpful in the future, if treatments were developed, and also helpful because there are supports available for certain diagnoses. After thinking it over for quite a few months, we decided to take his advice.

Honestly, we didn't really know we were having the test done. My daughter had a developmental delay and we went to a neurologist to have her checked out. The neurologist ordered several blood tests, an MRI, and an EEG. We just went along with the recommendation and didn't even know the specifics of what all the blood tests were for. No one specifically mentioned the words "Rett Syndrome" to us until the test came back positive.

It wasn't just about choosing to get the test done, it was about finding a diagnosis.

Because we suspected that she had Rett Syndrome, but [the] prominent neurologist in [our] area had doubted [the] diagnosis prior to testing being available. He specialized in
Mitochondrial Disorders and was a researcher, and really didn't want to look at Rett Syndrome, saying "it wasn't a useful diagnosis, because it couldn't be cured." One of our best friends, an Internal Medicine doctor, brought us info on Rett Syndrome.

To rule out Rett Syndrome:

When we were referred to the geneticist on our first appointment he said that Rett syndrome had been suspected but after his assessment he 'hand on heart didn't think it was necessary' as it was not Rett syndrome. He arranged to see our daughter in 7-8 months time. At the next appointment he said he was now going to test her as her strongly suspected she had it. We were extremely angry with him as he had been so against it the time before.

I really requested it, because I was hoping to rule out Rett Syndrome. The more I read about RS, the more certain I thought my daughter had it. Most doctors disagreed, so I asked for the tests (mainly in the hope of ruling it out.)

We raised the possibility of Rett with our pediatric neurologist and testing for it, but he discounted it on the basis that our daughter was walking and had some words. 18 months later it was separately raised by a geneticist we were attending who had screened our daughter negative for microdeletions (because my wife has a balanced translocation) and then went on to test for both Rett and Angelman. We were keen to get a prognosis. I was unsure to what extent her refractive epilepsy was holding her back and if we got on top of that she would progress. We also were trying to spend most of our free time to do books with her, try to get her speaking (she lost her speech), encourage play etc, with a mixture of feelings such as guilt and time-ticking going on in our minds in the background, potentially also at the expense of time spent with our other child. Getting a Rett diagnosis meant that we would adjust our expectations and also the high level of personal resource and desperation as well understanding that the main problem was her difficult to control epilepsy.

We wanted to see if she had the MECP2 mutation because she did not exhibit many clinical signs of Rett.

Parents’ reasons for not obtaining genetic testing:

[I]t's not been offered. If we wanted it, we had to pursue it. Time and money become an issue.

Behavioral and physical examination confirmed Rett Syndrome years before the genetic test was available. That is more conclusive than a genetic test I think.

The affect of the genetic test results on the parents:

Disappointment - while all physical signs point to Retts [sic], her genetic test for it came back negative. At the time the genetic test wasn't 100% accurate so now the assumption is she does have Retts [sic], she was just one of the invalid test results.

First reaction was disappointment that she really DID have RS [sic]. Second reaction was relief over removal of any doubt. It allowed me to make an informed decision regarding
trying to have another child. It's also made it easier when pursuing other services (such as respite care, support from Department of Rehabilitative Services, and placement in state-run home) to have a confirmed diagnosis.

My daughter is 41 years old and I am 65 years old, so at this point it did not affect our family in any way.

In no way. We were already certain they would come up positive. If it had been negative that would have been a different story.

Well--no one is happy to find out about [R]ett syndrome! But at least we knew the truth. Then we could proceed to make intelligent decisions about our daughter. I know our older girls had some moments of worry about the "genetic" thing. So learning there's a difference between genetic and inherited, and learning about mutations set her mind at ease for her own children.

I have another daughter that has to decide if she will have children of her own, based on the information from the genetic test, she has decided not to get pregnant. She is scared she will have a RS [sic] girl.

Having a definitive diagnosis has allowed us to grieve the loss of a typical child and move on. We can now focus on getting the therapies and services needed to enhance our daughter's life, instead of wasting time and energy finding a cause. Of course, it is a very serious diagnosis [sic], and I wish it didn't have to happen. Under the circumstances, I feel that having an answer is preferable to not knowing.

It was the best thing we did; I was immediately so glad that we followed through. This is because there was so much support provided to us, starting with a phone call from [our daughter's doctor] the day after he gave us the diagnosis to make sure we were okay, and to connect us with [the support group leader] and IRSF. The Rett community/IRSF has been unbelievably knowledgable [sic], supportive and helpful.

The results led to our daughter's diagnosis, so at first we were shocked. We did not realize that there was anything that seriously "wrong" with our daughter. However, it was very helpful to have a concrete explanation for her developmental delay and not have to question whether the diagnosis was correct. The genetic test, I think, allowed us to quickly move past figuring out what was going on with her development and start focusing on how best to help her.

We were devastated, but grateful to finally know what we were dealing with. I sometimes think back on the times before we knew what we were dealing with--I liked the idea that anything could still happen, including miraculous, overnight recovery. Having a diagnosis is both sobering and empowering.

It was very difficult getting the results because it was positive for gene mutation/Rett Syndrome and it just confirmed our fears, however I would rather know what was the cause of my daughter's developmental disability than not have any answer. It gives a name to it, it makes your family now become part of a group of others who are in the same situation. You can seek out information on how best to deal with it when it has a name. We have become active in supporting research for Rett and in educating those around us.
It made me cry for a minute. Other than that, it didn't change anything. What changed it all was when her hands stopped working a month later and then the downward spiral ensued. It did help to have a label for it as we went through that process.

No more guessing. It made it easier to find doctors who know how to treat [it]. Just the fact of having a special needs child affects everyone; financially, socially, emotionally, spiritually, and physically.

Initially devastated. It is very hard to hear that your child will never have a "normal" life. Luckily we adore our little girl and so, while life will probably be more difficult for everyone at times, we will make our daughter's life the best it can be.

Genetic results confirmed [the] clinical diagnosis - it's impossible to disentangle the effects of each. Main impact initially was relief - my daughter was severely developmentally delayed, and I feared 'no diagnosis' more than I feared a diagnosis of Rett, because I wanted an explanation. I wanted to understand why she was the way she was, what we could expect for the future, and what she needed. Genetic confirmation of [the] clinical diagnosis was helpful in 'coming to terms', because it made the situation so clear.

I felt very sad and fearful initially but relieved to find something to base our further efforts on.

At first I was not that interested in the testing as I saw no advantage to knowing there was a genetic mutation. (Knowing it wouldn't change anything). After we got the results we heard of the Byrd experiment where Rett was reversed in mice and soon after about the upcoming IGF1 trials and now I realize that knowing the mutation is extremely important.

For us it explained all that had been happening to our daughter. Prior to that we felt some people didn't believe how good our daughter had been before her regression. We could definitely pin point her start of regression. It also made us realize that we had to prepare for the future as our daughter was never going to achieved [sic] certain goals now such as walking. We realized we had to move to a more suitable home.

Where to [sic] you begin with this?? Rett syndrome rocks your world and makes you change all you know about parenting. Having the genetic testing have [sic] helped with having an answer to our daughter's challenges.

I think it would have been much more traumatic to have the diagnosis if her period of regression hadn't pretty much passed already.

Divorce and relocation [sic].


The genetic testing did not affect my family Rett did. How has it affected our family, if you can think it than it was affected. Meals, days, nights, outings, vacations, birthdays, holidays, Sunday mass, school awards for my other kids, people or family coming over if
they are sick, then forget it we would let them come over, because she'll end up with pneumonina [sic].

Getting the diagnosis was a shock. There was a mix up between testing and reporting the results to everyone, including me and I didn't find out she had Rett Syndrome until a year after the test was done. It wasn't broken down to me or explained they just printed the results that said she had it and sent me on my way. I felt like I was hit by a truck but at least I know what she has and have a really amazing support system through RettNet.

It gives you the final answer so there is no more guessing even though she has all of the symptoms. It was devastating at first, but as the years have went on it seems easier to deal with but you still remember the phone call and the date of it when the results came in...

Life altering

It's membership into a club we never wanted to be in but we focus on the girl not her traveling companion.

One result was that we realized our daughter was not severe MR as we were initially told prior to test results. We then treated her like she understood, which resulted in her becoming much happier and less frustrated. She also gained speech and other communication abilities, and was eager to demonstrate how smart she is because she was confident we were listening.

No more children of course. My oldest daughter has decided to not have children (She is 16 years older than our Rett child)

"d" day is one I will never forget. Our neurologist and geneticist met us together and told us [our daughter] had Rett syndrome. They said over time she would basically become a vegetable. We were horrified and crushed. However, I'm happy to say that although their diagnosis was correct, their prognosis couldn't have been more wrong. Our daughter is thriving and actually gaining skills.

How parents used the genetic information:

Another daughter requested testing based on R.S. [sic] daughter's test result. Also, the information helped in obtaining some care giving services from outside the home.

Our information is with some of the researchers. Our use of the information is strictly to promote more genetic testings [sic] for girls who do not fit the description. There are many girls in the world like my daughter who are misdiagnosed and being hurt by treatments that will not work on them. My daughter was on ADD trials for over a year before her diagnosis and that year was the worst year of my life; she was not my little girl. She became a monster and no one could explain it so they kept changing meds and boosting dosages. After she was tested for the gene we learned that the meds used on her were hurting her.

Genetic confirmation of Rett has been useful in explaining my daughter's condition to education, welfare and other services. I have also sought information on my daughter's specific mutation - to try to learn more about the correlation between genotype and phenotype, and to help us decide where to focus our efforts and resources.
We pursued the top specialist familiar with the disorder. We read extensively. I believe the information helped us be better prepared when she first presented with seizures. The diagnosis helped with insurance coverage and obtaining needed services. We also raise funds for a cure.

Although our daughter was 16 when we received the results, it opened up a plethora of information on her condition and a connection to others with the same issues.

It came together as both a clinical and medical confirmation of the diagnosis. [Our daughter] was no longer considered PDD NOS but nothing changed in her schooling. We were able to being monitoring her heart and watch for scoliosis and seizures as these are known symptoms that [our daughter] had not manifested at the time of the diagnosis. WE KNEW WHAT TO LOOK FOR!

Having a diagnosis has made professionals dealing with her accept that certain things are not achievable [sic] and have change they treatment. For example the SALT would always insist on trying to get our daughter to use sign language even though we knew she would not. After diagnosis she accepted it and changed her treatment. It has also helped in applying for benefits and grants as people now accept she is disabled for life.

I haven't had any use for the testing myself. I now have more questions than answers.

We use the information for reports that we have to do with the Social Security office or the local mental health facilities. I also used the information to go and talk to a genetic counselor who was very informative and helped me understand what happened and the extent of what Rett syndrome entailed. Looking back I wish that when I got the test results the genetic counselor was the one I met with. He was so informative and made me feel like finally someone understood what I was talking about.

For one, state and county services. Sometimes there are problems obtaining services without a confirmed diagnosis. Two, if we can help in any way with research and promoting awareness about Rett Syndrome. Then the confirmed diagnosis definitely helps.

We used the information of the rare re-occurrence to choose against in-vitro testing while pregnant with our second child.

We have not done anything with the genetic testing other than advocate awareness within the medical community. If the 5 neurologists who had assessed our daughter had been more educated and aware, and not dismissive of my concerns and the research that we had done, we would have gotten an earlier diagnosis which may have altered our daughter's future. When our daughter entered the hospital in 2003. she never came home. She remained in the hospital for the next three years enduring unbelievable complications, we believe, as a result of the consequences of the stress from the surgeries. She died in 2006 at the age of 13.

**Reasons parents would still get testing knowing what they know now:**

Knowledge has given me the power to be my daughter's advocate. I speak as she can't.
Yes but much sooner it was so difficult to not understand what she needed. No one seemed to know, including a top Neuroloigst [sic] at TCH in Colo. Our Ped[iatrician] doc[tor] even said she dismissed the idea because she had a patient afflicted with Rett and they were nothing alike. Her early intervention teacher thought she had Rett but couldn’t tell us? Our Family didn’t tell us Julie had Rett or we would of had Victoria tested immediately.

Better the devil you know.

My daughter deserves the best care possible. I’m glad the test was done I do not like how it was handled I was called on the telephone by her neurologist did not know what rett syndrome was she just told me my daughter may never walk and never go to a regular school she will be special needs and to look it up on the computer.

Retts was the last thing i thought my daughter had because she does not fit the physical description of it. I waited an entire year before getting the test done because I thought it was impossible for her to have it. Knowing what I know now I would have done it right away.

Yes, but having the diagnosis can sometimes be a disadvantage compared to having a diagnosis of autism or CP for example in terms of getting services as perception of a much more severe diagnosis, still considered degenerative by many docs[tors] institutions.

You can’t know in advance how you will feel. I told the Pediatrician it wouldn’t change anything. In fact it allowed me to "finish" grieving and start living/ helping.

There is NOTHING worse then not knowing. We were dx's [sic] of Autism, CP, and Global developmental delay, all that NEVER seemed to fit.

It is much better to fully understand what condition your child has, even as devastating as it was, than to be constantly searching for the reason things weren't developing as normal.

I would have insisted our pediatric neurologist testing earlier. His concept of Rett seemed to have been only the very severe variant. An earlier diagnosis would have altered how we approached our family situation, in particular, the extent to which we would hold our breath on our child improving on a day to day basis.

Parents’ views regarding the usefulness of genetic testing for RTT:

It can be helpful but at my daughter's age of nearly 30 years, it doesn't seem very relevant anymore except to educate my other 3 daughters.

It’s obvious, the discovery of the mutation would probably not been found in my lifetime if it had not been for those very generous parents and girls who allowed the multitude of testing to be done on them.

I think that the usefulness is important regarding science, research, and the decision to have more children. In our own personal case, (daughter's age, length of time w/o a diagnosis), the importance of the testing would now be with my other daughter and her decision to have children.
It helps the credibility of Rett Syndrome as a disorder for insurance, educators, therapists, doctors, etc.

At her age it really didn’t matter much. But when she was young we needed a good diagnosis in order to get services for her. When I read her the letter with the results of the genetic test, she looked at me and her eyes said ‘yeah, I know, where have you been?

Rett syndrome is not a behavioral disorder and therefore demands more than a clinical diagnosis to learn more details of the disease. Hopefully, some day such knowledge will direct us to better treatments.

I personally like the fact that we stumbled across the diagnosis of Rett Syndrome in the early days due to a newspaper article about another Rett child describing all the clinical aspects of Rett Syndrome that [our daughter] exhibited also. It was completely obvious that [our daughter] had Rett Syndrome according to the clinical criteria. I can't say how I would have reacted had it been a blood test and then a diagnosis. I think reading someone else's "history" and feeling like we wrote it was more profound that just getting a positive test result back. I am the type of person who likes to "make sure" so having a genetic test for RS is definitely icing on the cake for us.

As far as my daughter goes, she has all the classic Rett symptoms, so diagnosing her by symptoms at age 3 was pretty positive. But for some older ones whose symptoms have changed or very young ones whose symptoms may not have started, genetic testing would be very beneficial and I would want my daughter to participate to help others.

Genetic testing will allow parents for earlier diagnosis of the disorder. This helps them to know which therapies to pursue and which are unlikely to help. It alleviates the guilt associated with having a child with special needs.

Because there are other conditions with mutations of the same gene I feel there are girls currently diagnosed who do not actually have Rett.

We spent a year and a half seeing Dr. after Dr. in an effort to find a diagnosis. If even 1 family can be spared all that pain genetic testing is worth everything.

Clinical symptoms are very general. Rett syndrome is very similar to other diseases for example Angelman syndrome. It's a reason for which they are so important genetic tests.

I like facts and want to see on paper I kinda [sic] get offended if someone looks at my kid a says oh they have Rett syndrome with out facts

I think a definite answer would be needed, if a doctor had given a diagnosis as severe as Rett syndrome without actual proof I wouldn’t have accepted it, i actually nearly asked for a second test so I didn’t have to believe it at the time

With a genetic test for Rett Syndrome there are no "what ifs". You know for sure what you are dealing with, without any doubts. With a Clinical diagnosis I/you would always wonder "perhaps it isn't Rett we are dealing with. Perhaps we are missing something, a cure, a treatment that would be different than a Rett treatment." Although there is not a
cure or treatment for Rett Syndrome, yet, I do believe that one day there will be, with a genetic diagnosis there are no doubts.

Clinical trial has human error. Genetic testing, making an error is very unlikely. And results are more convincing.

We had been pursuing testing for two years before the genetic testing for Rett syndrome for my daughter because at the time she did not meet the clinical diagnosis until age 3-31/2. Until that point she was subjected to MRI's, CT scans of both spinal cord and brain, blood work, and two EMG's, one of which was in the OR under heavy sedation. Genetic testing confirmed the diagnosis and would have been easier, less painful and potentially less costly then two years of searching.

Mostly my concerns are for the girls whose tests come back negative -- they are told they don't have Rett -- they do not know there are several levels of testing or are not able to get into a protein study --

The above questions are hard to answer - largely because it depends on the expertise of the person making the clinical diagnosis! My daughter was diagnosed by a specialist in Rett - therefore I had a high level of trust in her judgment. I 'knew' before she was diagnosed that she had Rett, because she ticked nearly all the boxes - but I wanted it to be confirmed (clinically and genetically). If a neurologist with no particular expertise in Rett had told me either that she did or didn't have Rett, I wouldn't have been satisfied until we had a clear genetic result. As it is, the genetic result confirmed the clinical diagnosis - which is what we expected. My daughter has a common mutation, and knowing this enables us to understand her better and to be better informed when it comes to obtaining services etc. I think my bottom-line view is: if a reliable test exists, I want it.

It is necessary and valuable not only to the parents/caregivers, since different mutations may have different outcomes and treatments, but also to the field, since comparison of genotype and phenotype can be revealing.

Genetic testing holds more weight for those in the medical and insurance community who need a diagnosis to provide what they're supposed to.

The previous question asking about previous diagnosis and the follow up questions assuming it was a misdiagnosis is misleading and wrong. Some people are affected by multiple diagnosis. For instance, my daughter has a mitochondrial disorder. It is not a misdiagnosis, nor did it have any effect on my decision to have her tested for Rett Syndrome. It is also a way for researchers to connect dots and see how one will/can affect the other. I understand that some people are misdiagnosed with other disorders, but some actually do correlate. Please take this into consideration.

We knew she had Rett Syndrome before The genetic testing was done. She had all the signs. We just wanted the clinical diagnosis to confirm it.

It is concrete and doesn't have the percentage of error or subjectability [sic] that a clinical diagnosis does. The clinical diagnosis was a great tool for confirmation.

It's both important they complete each other
I believe that clinical diagnosis can be subjective and not as concrete as genetic testing and even though genetic testing can be wrong in a narrow margin of cases I think more cases can be misdiagnosed. My daughter was diagnosed with two other syndromes clinically and neither were the right one so I think genetic testing is extremely helpful to the parent and to the Rett community as a whole.

Rett Syndrome still needs to be initially diagnosed clinically and then maybe confirm by a genetic test, not the other way particularly since we are still learning about the gene itself.

I believe that the positive results are accurate and conclusive. However, I think that a clinical diagnosis is important to address the specific needs of each child since Rett manifests itself differently despite the same mutation.

At the time our daughter developed her epilepsy just before age two, we were about to embark on pre-implantation genetic diagnosis/HLA-selection/IVF for a 'saviour sibling' for our son with Fanconi Anaemia who doesn't have a bone marrow donor match. We could have really done with the genetic clarity much earlier rather than quite late in our IVF, i.e., after five cycles. From my perspective as a neurosurgeon, I felt that my pediatric neurology colleagues were clueless to anything but the very classic severe picture of Rett. I think the strict interpretation of the clinical criteria may often be used to exclude potential Rett-affected girls, in particular where the regression is milder or as in our case the apparent predominant part of the picture was refractive atypical absence epilepsy (about 300 events in 24 hours). Certainly, in my own professional practice, a suspected genetic disorder should be always underpinned by a molecular genetic diagnosis, in particular in the context of prospective evolving therapies such as PTC124.

Regardless of the mutation, Rett Syndrome is Rett Syndrome. Two girls with the exact mutation may have widely ranging symptoms and expressions of that mutation. Short of getting the testing so you can access services, it wouldn't matter. Due to its random nature it's rare to have more than one child carry it - I told my other daughter she could get tested when she becomes of child bearing age but I don't think it's necessary.

I hope genetic tests will be found for all Rett mutations. I have talked to many parents who I believe symptoms of their daughter were Rett, but after negative genetic test they did not seek clinical diagnosis or Dr. [sic] did not look at criteria. There are many families out there still in the dark because all tests are not yet available.

For me personally, having the genetic results felt far more concrete and real. I do know other families that have tested negative on the genetic test and clearly their daughter is displaying all of the Rett tendencies and so the clinical diagnosis is as good as it gets. I think I would still have that doubt, but that is me personally.

When children are younger, they may have different origins of developmental issues and "look" similar in many ways, and you can easily be misdiagnosed... if you know, earlier, what you are dealing with, you may get better services, treatments, help, etc... and you can team up with other parents dealing with the same issues.... it's way better to know in terms of planning for the future,,, and essentially helping your child... that's what it comes down to... to get the best help for your child sooner rather than later.....
I do put more trust in the genetic diagnosis. It is ‘blind’, that is, the diagnosis is not influenced by a physician’s experience or bias and not by parents’ observations.

[I] thought that [genetic testing] was wonderful for younger parents and children just starting out on the ‘Rett road’ but we had already gone down that road and had pretty much realized that is what our daughter had all her life and was [sic] just getting use[d] to calling it something, Rett syndrome.

Remaining Thoughts:

Hopefully there will be more availability to genetic testing so that families can make informed decisions. Observing the heartache for 23 years, the daily struggles, the sacrifices, the physical pain that we feel when we see our daughter suffer day after day, has affected her brothers deeply. The struggle never ends and we have lived, gladly and with love, for just an occasional smile, but cannot allow this wrenching devastation to possibly continue into the next generation.

If genetic testing is negative, parents should be sure to pursue the clinical exam.

Your assumption that parents either declined or accepted the test is not fully correct. Most of the dozens of parents I know have never been offered genetic testing.

I would highly recommend that every parent not only consider but have genetic testing done on their child who they suspect has Rett Syndrome. Future studies will demand what type of mutation a child has in order to receive therapy or treatments that could lead to a cure.

I think that a genetic test is given more weight by the educators and even some in the medical profession, but I am satisfied with the clinical diagnosis.

My daughter is now 41 years old. It would have been helpful to have this information in the 1970's, but we did not and so it made it very hard to understand what was happening to her at the age of 2 in 1971. We had no knowledge of Rett Syndrome at the time in history.

Genetic testing gives you some of those answers. It is important for your family's future growth and your children's children. But what it also does is put limitations and reduce expectations for those parents who cannot get past the severity of what they have been told. It lets educators put limitations on your child's ability to learn and keeps them from experiencing every bit of life that their peers have. It takes very strong willed parents to buck the education system and the insurance companies and get their child what they are entitled to for a lifetime. Most of the time if there are no labels people will never stop trying to find a fix for what is wrong and doing everything in their power to help their child succeed. I was lucky that way. Since I had no genetic tests early on, my daughter went thru grade school and part of junior high without hearing or understanding the limitations of a Rett diagnosis.

I know of some children that were assessed with genetic testing many years ago and were told the diagnosis of RS [sic] was negative. I wish that more information regarding more
updated testing was available to more doctors and parents so that these families could be more comfortable in what they are doing for treatment for their daughters.

As the research being done around Rett Syndrome advances, it seems that it will be more and more helpful, if not necessary, to know what specific mutation underlies each case of Rett Syndrome in order to more effectively target and treat the disorder. And actually, thinking about it now, I value the genetic testing as much or more than the clinical diagnosis for this reason, contrary to my earlier answer. Also, I feel that if we were in a different part of the country, no one would have recommended the comprehensive MECP2 testing since the clinical diagnosis was not obviously Rett.

Please don't ever give up doing genetic testing for Rett Syndrome. As humans we need to know for certain, we can not live with "perhaps it is this or maybe it is that or your child seems to have Rett Syndrome". A clinical diagnosis is good when the genetic testing comes back negative, but I believe it should always be tested first. It gives a parent a place to start, this is very important when dealing with an illness of your child/children.

[Our daughter] was diagnosed first with SCAD, A fatty Oxidation Mitochondrial disorder. That was in the exception criteria for Rett. It turns out she did have both along with other girls so it should not be an exclusion criteria. One Dr. [sic] missed the Dx [sic] based on this but others didn't.

I believe all babies should be tested at birth. Not knowing what was causing such severe and heartbreaking losses to my child almost killed me.

For us, the timing was good. As I said earlier, I think it would have been horribly earth shattering if we had the diagnosis before her regression, but by the time that we received it, we already knew that we were dealing with something huge. On the other hand, if we had received the diagnosis earlier, we may have been able to have had a shorter period of grief time - more like ripping a bandaid [sic] off instead of peeling it back little by little with a long period of pain and uncertainty as to "what was next".

Too bad it's so expensive to do natally [sic]. I got tested for Down Syndrome because I didn't want a special needs baby if I could help it. But, oh well. I love her.

I feel that genetic doctors should advise patients to take out a life insurance policy on their child before any genetic testing is done. It may sound crazy but, once your child has a Rett diagnosis you can't get a life insurance policy on them. It may be a sad topic to bring up but it needs to be addressed.

I think it is a test that should be done ANY time there is any type of regression.

I would recommend it as a tool to help other parents understand and educate themselves

It should be available and affordable to everyone who needs or wants it. Testing doesn't always give us the answers we need but it does help. The genetic testing should include BDNF and CDKL5 in addition to the MECP2, in my opinion, since the result is pretty much the same to live with.
I would really like to see parents receive more information with the diagnosis and how to help. I probably spent the next eight weeks tracking down information about the mutation and did not understand the impact of x inactivation until completing a lot of reading, and talking with other parents. - I wish doctors were better able to explain results and the implications.