# How to Conquer a Chromosome Abnormality—
# What is our strategy for identifying treatments?

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## Special points of interest:

* Clinical Assessments
* Natural History
* Key Genes
* Critical Regions
* Treatments & Therapies

## Inside this issue:



## Identifying Treatments

Our global strategy following three broad paths is parallel, with each informed by the others. These broad areas are clinical assessment, identifying key genes, and changing gene action.

Here at the Chromosome 18 Clinical Research Center, our top priority, thus far, has been to perform clinical assessments. These assessments provide critical information about the conditions involving chromosome 18.

- **Clinical Assessment**
  —descriptive & natural history
  —standard symptomatic treatments
- **Identifying key genes**
  —eliminate dosage insensitive genes
  —critical regions > candidate genes
  —newly identified disease genes
- **Changing gene action**
  —treatments & therapies

## Clinical Assessments

While the clinical assessment does not sound like cutting edge science that captures everyone's imagination, it is a critically important step on the road to treatments. Clinical assessments provide information on the nature of the condition and how it changes over time. They also tell us about which treatments and therapies are currently being used and their effectiveness.

- **Descriptive**
  —Comprehensive assessment
  —Condition description
- **Natural History**
- **Standard symptomatic treatments**

## Comprehensive Clinical Assessments

Comprehensive clinical assessments of a large number of people with each condition is paramount. On the surface, these assessments may seem like ones done by local physicians. They involve MRIs, physical exams, detailed medical and developmental histories, and other exams that most study participants have had prior to visiting the Research Center.

However, these evaluations are fundamentally different. Most doctors respond to questions and concerns from you and that directs their evaluations and testing. We perform comprehensive evaluations based on everything we know from the medical literature, our review of participants' medical records, and our own knowledge of and experience with these conditions.

These assessments benefit the participants as well as the Research Center. The family learns from experts about their child's specific needs and strengths, and how they are doing compared to others with the same conditions.

Once a group of individuals with a condition has been assessed, the information is compiled in a standardized format allowing us to compile a comprehensive and cohesive description of the condition. For example, all hearing tests will be done in the same way with the same measurements and standards, so the information gained from each of the participants is comparable—a critical step in gaining thorough understanding of a condition.

## Natural History

Clinical assessments also help us compile data about the natural history of a condition. This helps us understand how a condition manifests over time—how it changes as the person gets older. This information is gathered in two ways.

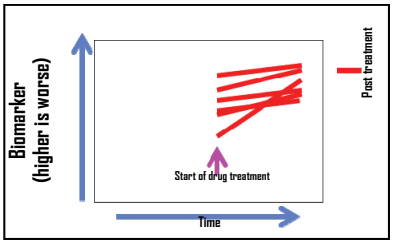
First, by assessing individuals with the same condition who are different ages, a general idea of the natural history is realized. The second approach is longitudinal in nature, meaning we follow many individuals as they grow up and grow old—preferable approach but takes many years. While accumulating natural history data in this longitudinal manner, we also use data gathered from different persons at different ages as proxy for natural history.

## The Importance of Natural History

Here is a hypothetical example to explain the importance of natural history. Imagine that we think we have discovered the cure for Disease LMNOP. We have a biomarker to measure to determine if this drug therapy works. A biomarker can be anything measurable that relates to the course of the disease—a measurement from a scan or the level of some chemical in the blood.

The higher the number of our biomarker, the more severe the disease is and the more it has progressed. We want to develop a drug that keeps that number from getting higher. LMNOP is a rare disease so we don't have a lot of participants from which to gather our data.

This graph show what happens to our




biomarker measurements when six people are treated over the course of the study. Did this drug work? The biomarker measurements got higher, so maybe the drug was a failure. A successful drug would have a horizontal line or even one that decreased.

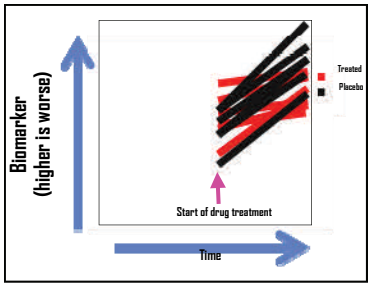
However, we don't know if the biomarker measurements would have increased without the drug. Perhaps the drug actually keep the disease from getting as bad as it would have without the treatment. Given just this data, it is impossible to know whether the drug was successful.

**"Successful treatment trials can be dependent on years of natural history data."**

A better way to test the new drug is to give a group of people a placebo—a sugar pill, for example—and track the biomarker in them as well as in the treated group. This allows comparison of the outcomes for people who were treated with those who were not.

In the graph, it looks like most people who were treated actually did do better. The change in the biomarker was not stopped, but it did show down compared to the untreated placebo group. Now do you think the drug worked?

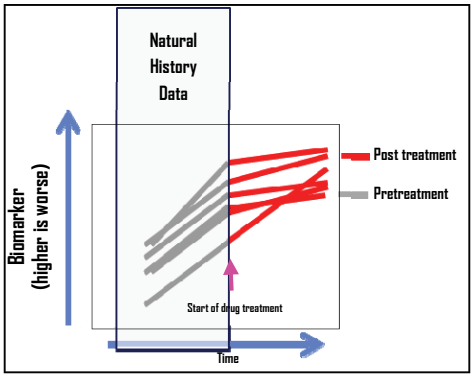
The disadvantage of this study design




is that it takes twice as many people which may be a problem in a rare disease. Also some people in the study will not receive treatment. People enrolling in the drug trial will have to be informed that they might get a placebo and that their disease might be worse instead of better. It may be difficult to get people to take that chance and may depend on what other treatment options are available as standard care.

The better option—especially with rare disease—is to use natural history data. In this study, all of the individuals in the study had previous biomarker data from before the treatment trial began. You can clearly see how the drug affected each individual person and it is very clear that the drug made a big difference for almost everyone. In addition, everyone in the study was treated and few individuals were needed to complete the study.

This successful treatment trial was only possible because data had been gathered




on potential study participants for years before any possible drug treatments were developed. This emphasizes the importance of gathering clinical assessment data with an eye for potential biomarkers. A biomarker does not need to be the exact endpoint you desire, but it needs to correlate with your endpoint. It is an indicator of a biological state. And since the identification of potential biomarkers can come from the clinical assessment, the importance of clinical assessments is evident.

## Standard Symptomatic Treatments

The last reason to perform clinical assessments is to identify standard treatments. There may be treatments that are commonly used in the general population that have simply not been applied to people with chromosome 18 conditions. For example, when we started our studies, the literature said that everyone with 18q– and 18p– were short. For twenty years no one had investigated the cause of their short stature. We found that they were short because they had growth hormone deficiency which is a treatable condition—never before applied to people with chromosome 18 conditions.

In addition to identifying standard treatments, we also compare how study participants are treated for some of the same conditions. In this way we can identify best practices and treatments for persons with these conditions. For example, if we learn that everyone with condition X responds to one class of anti-seizure medications and few respond to another class of drug, this would be useful information in the treatment of seizures for people with condition X.

To reiterate, while the clinical assessment does not sound like cutting edge science and does not capture everyone's imagination, it is a critically important step on the road to treatments.

## Identifying Key Genes

The second track of investigation is focused on understanding the molecular basis of the chromosome 18 conditions. We want to understand more about the genes involved with chromosome 18 conditions.

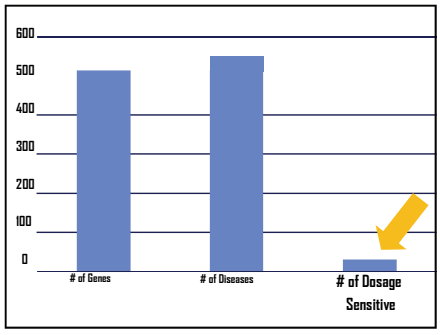
We operate under the premise that if we discover the key genes on chromosome 18, we can understand what is happening on a molecular level—allowing us to progress in our development of very specific treatments. These treatments would likely be more effective and have fewer undesired side effects.

**Identifying Key Genes**

- Eliminate dosage insensitive genes
- Critical regions > candidate genes
- New identified disease genes

**"We estimate that for 18p– and Tetrasomy 18p there may be only 4 to 8 key genes, and for 18q– there may be only 5 to 9."**

## Eliminating Dosage Insensitive Genes




Luckily, we do not need to understand the function of every gene on chromosome 18. We only need to be concerned with the function of a small number of the genes—the ones that are dosage sensitive. By dosage, we simply mean the number of copies of a gene.

We know from work with fruit flies, mice and from some human conditions, that only about 5 to 10% of the genes will cause a disease or a problem when an abnormal dosage is present—one copy instead of two or three or four copies instead of two. Our challenge is to identify these key "dosage sensitive" genes.

We estimate that for 18p– and Tetrasomy 18p there are probably only four to eight key genes, and for 18q– there may be only five to nine.

We identify these genes using multiple strategies. The first step is to identify what we already know about the genes on chromosome 18. We keep track of possible gene dosage effects of every gene on chromosome 18 by continuously and systematically searching the latest medical literature. We compile this information in our Gene Dosage Map. Unfortunately, very little is know about the gene dosage effects of most genes at this time.

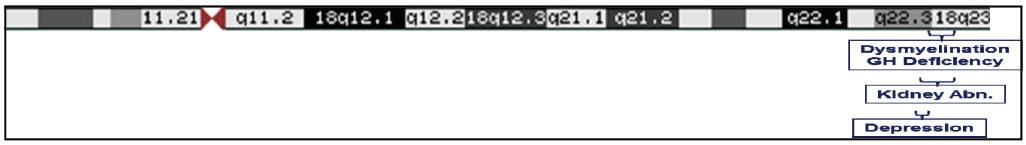
However, some genes can be eliminated from concern or at least put on the "unlikely" list using criteria about the disease associated with those particular genes. Also if a gene is located in a region that has normal variation in the gene copy number, meaning that average people have been identified with deletion of duplications of a certain gene, then it goes on our "unlikely to be dosage sensitive" list as well.

## Critical Regions > Candidate Genes

We also correlate our gathered clinical data with specific regions of chromosome 18 that are duplicated or deleted in our study population. For example, by identifying a region of the chromosome that is deleted in everyone with a certain symptom, we can postulate that the genes causing that symptom is in that critical region.

We have identified regions associated with dysmyelination of the brain, growth hormone deficiency and depression. We do not know yet which genes in these regions cause these problems, but we have narrowed down to just a few genes in each case. Work is ongoing to identify the exact genes causing each of these features.

**"There is lots of potential for normalizing the lives of people with chromosome 18 conditions."**




## Newly Identified Disease Genes

In a couple of cases, these critical regions have already been narrowed to a single gene. This is the case for aural atresia—when the ear canals are closed before reaching the eardrum. We also know the gene responsible for expressive speech delay in persons with proximal 18q-. As time goes on, known conditions are identified to be caused by a duplication or deletion of a gene on chromosome 18. This is the case with Pitt Hopkins syndrome which was found to be caused by a deletion or mutation of the *TCF4* gene.


Once the key genes are identified, then cutting edge science can begin. We can investigate mice that have deletions or duplications of these key genes—helping us to understand the cellular processes that have failed. We can also use these mice to develop and initially test potential new drugs.

## Treatments and Therapies

The final step of getting answers is discovering how to change gene action—to get one gene to do the work of two or to get three or four genes to only do the work of two.

We always talk about therapies in the broadest of terms. A magic bullet drug to make a condition go away would be great but is unlikely to happen. We are asked often about possible gene therapy but there may be much easier things we can do.

With chromosome abnormalities in which we need to correct several genes, we are likely to employ many different therapies. In addition to drug therapies, there may be exposures to be avoided; such as, medicines that could be more toxic or have higher potentials for side effects. There could be dietary restrictions as well as dietary supplementations that could be helpful. As we understand specific mental deficiencies, there may be very targeted experiential therapies that take advantage of the brain's plasticity. One example is Fast ForWord© which trains the brain to process sounds faster and thereby improves reading skills.

* **Drugs**
* **Exposures**
* **Dietary**
* **Experiential**

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**Our Motto**
**To provide individuals and families affected by chromosome 18 abnormalities with comprehensive medical and educational information with a focus on treatment options.**

**We are on the web!**

**http://pediatrics.uthscsa.edu/centers/chromosome18/**

Information provided by The Chromosome 18 Clinical Research Center to:

The Chromosome 18 Registry & Research Society

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