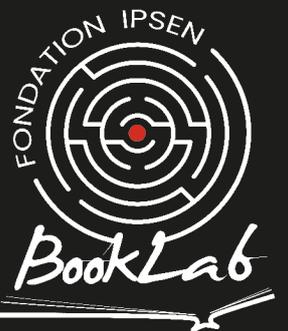


The Rare Disease Gazette

*Conversations with
the world's experts
about rare disease*

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Editorial

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Rare Disease Detection: Rare But Not Alone



The plight of patients with rare diseases is a critical unmet need of patients in health-care. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public. In 2021 these webinars focused on improving the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine



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Experts of the month

Monica Wojcik, MD
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Melissa P.
Wasserstein, MD
James R. Bonham, PhD
Sean Sanders, Ph.D.

Sean Sanders (host):

Hello and a very warm welcome to this fourth installment of the Science and Life Webinar series on rare diseases. I am Sean Sanders, Director and Senior Editor for Custom Publishing at Science, and once again, it is my pleasure to be the moderator for today's many different aspects of this important topic of rare diseases. If you missed our previous webinars in this series, you can find them archived at webinar.sciencemag.org. For tweets, you can add the hashtag #ScienceWebinar. We pre-recorded this webinar a couple of weeks before broadcasting, so we are not able to take questions from live viewers, but as always, we will do our best to cover this topic as completely as possible. Finally, thank you to Foundation Ipsen for sponsoring today's event and this series.

I am pleased to welcome today's panel of experts, and give them the opportunity to introduce themselves. A very warm welcome to all of you, thank you for making the time to join us today, and Monica, I am going to ask you to get the ball rolling.

Monica Hsiung Wojcik:

Thank you, Sean. My name is Monica Wojcik. I am a medical geneticist at Boston Children's Hospital, and I am also a neonatologist here taking care of neonates and infants in the intensive care unit. In addition to my clinical role, I also spend a lot of time doing research related to diagnosis and the pre and postnatal periods, and research related to genomic medicine or how we use these diagnoses to really empower and inform the best care for our babies and their families. Not only in the NICU, but in the neonatal infant period and beyond.

Sean Sanders (host):

Next, I am going to turn to Roberto.

Roberto Giugliani:

My name is Roberto Giugliani. I am a medical geneticist based in Porto Alegre, just south of Brazil, where I work in the University Hospital and have been involved over the last 35 years with newborn screening, trying to bring this kind of approach to Brazil and Latin America and working also in preservational research to innovate all these areas in our region. As a medical geneticist, I have also been involved in prenatal diagnoses and prenatal screening.

Sean Sanders (host):

Next up is Jim, who's joining us from the UK.

Jim Bonham:

I am President at the International Society for Neonatal Screening. We have around 500 members in that society, drawn from a little more than 40 countries right around the world. In my day job, I work as laboratory lead for newborn screening in the UK, and one of the exciting ventures that we are about to embark upon is screening for a new condition in the UK, at least evaluating that severe combined immune deficiency. That is one of the disorders which causes immune problems in young children, we can avoid if we identify early. So that gives it kind of flavor of the exciting things that newborn screening can sometimes deliver.

Sean Sanders (host):

Finally, we are going to ask Melissa to introduce herself.

Melissa P. Wasserstein:

I am a medical geneticist, and I work at the Children's Hospital at Montefiore and the Albert Einstein College of Medicine in the Bronx, New York. I am specifically a biochemical geneticist, which means that I take care of patients with inborn errors of metabolism, most of whom were diagnosed through newborn screening, so that they recognized that full benefit of early detection. For my research, I work with a pilot newborn screening research study called ScreenPlus, where we are screening consented babies for an additional 14 disorders, while we are also doing an evaluation of the associated ethical issues that accompany newborn screening for complex disorders.

Sean Sanders (host):

Jim, I think I am going to have you start us off, and before we get to the importance of neonatal or newborn screening, I wonder if you could just walk us through what is neonatal and newborn screening, and how is it done?

Jim Bonham:

Newborn screening gives us the opportunity to identify children before they become ill, and that is pivotal. When these children are born, they look very often, perfectly normal. They behave entirely normally and unknown to anyone, they have a serious and sometimes life-threatening condition, and what newborn screening enables us to do is to detect that before they become ill and intervene and treat them, and that treatment is truly life-changing for those children.

In terms of the organization of newborn screening, it was first described really back in the 1960s - so we have been doing newborn screening now in countries like the US, and in many countries in Europe for more than 50 years. One of the early pioneers was a chap called Dr. Robert Guthrie. Robert Guthrie was a microbiologist, and he gave us not only a test that could be used in newborn screening, but perhaps even more importantly a means of obtaining a sample and transporting that sample simply. The condition he was interested in is a rare disorder, occurs in around about 1 in 10,000 children called phenylketonuria, often abbreviated to PKU, and what Bob Guthrie discovered was that you could identify those children affected by a simple microbiological test.

That test has since been replaced, but what he gifted us was something even more enduring. That what he gifted us, as I say, a means of collecting that sample, and what Bob Guthrie suggested was that you could take a tiny drop of blood, drop it onto a filter paper and allow that to dry and then transport that sample simply and easily to a regional testing center. That is basically the heart of the newborn screening that we still do today. Of course, now we test for many more conditions, and we use more sophisticated technology, but the basics of that was set by Bob Guthrie in the 1960s.

Sean Sanders (host):

So essentially, the test hasn't changed. It is still a pinprick with a young newborn, and a paper card that the blood is put on?

Jim Bonham:

Yes. It is still a pinprick of blood, just effectively one drop of blood, usually a few drops of blood applied across a filter paper with the patient's identification details attached to that. That can be air dried and then popped into an envelope and sent by FedEx, or by any other mail system to a regional testing center. Of course, the quality of the sample is important. It is important to get it to the laboratory quickly, but the samples are pretty stable, and that really forms the bedrock of newborn screening right around the world.

Sean Sanders (host):

A couple of you mentioned some new advances in newborn screenings, and new programs that you are involved in. Melissa, maybe I can come to you and ask you, what are some of the recent advances in newborn screening, and what are you seeing for the future?

Melissa P. Wasserstein:

We started out in the 1960s screening for one disorder and that was PKU, and the reason why we did that was this acknowledgement that PKU, you can pick it up on that tiny little bit of blood. You can intervene if the child has a positive screen, so you can really make a tremendous difference in a child who otherwise would have had significant intellectual developmental disability. And you can do it in a cost-effective manner. Since then, that tiny little bit two to three-millimeter punch of blood on a filter paper, we can now screen for over 50 disorders on every baby, using that same tiny little bit of blood.

That is where the major technological advances have been in terms of the ability to use different machinery, different technologies, and get even more information to try to make early diagnosis. In addition to doing those tests, we can also do different types of testing on that dried blood spot - including DNA-based testing and genomic-based testing. The changes and the improvements have been vast and really exciting to see.

Sean Sanders (host):

Roberto, there are a couple of questions that I was interested in having your input on. The one is in my background reading around rare diseases and neonatal testing, I was surprised to read that it is essentially different in almost every country, how the testing is done,

the number of diseases tested for. Is that something you could speak to, and talk to testing in remote locations where it might be difficult to get the samples to a hospital or a testing facility quickly.

Roberto Giugliani:

You are right, the panels that are in place in each country, they are quite different. You take the US: from state to state, there are some differences, but generally they are the same so it depends very much on how the health system deals with this program, their priorities, what they decide that should be included. As Melissa said, with the number of conditions that we could include in this the newborn screening is potentially unlimited, but of course, you have some pre-conditions to define which this varies from country to country.

There are some countries with very limited panels and other countries with more expanded panels, and there is a lot of heterogeneity among these programs. I think the different experiences could be combined. The International Society of Newborn Screening is trying to have more uniform panels, or at least some minimum steps and conditions that should be to be included in the worldwide program.

Sean Sanders (host):

Roberto, is testing global? Is every child in the world tested, or are there still parts of the world where no testing is done?

“Unfortunately, there are still some parts of the world where no neonatal testing for rare disease is done.”

Roberto Giugliani:

Unfortunately, there are still some parts of the world where no neonatal testing for rare disease is done. Most developing countries have screening, but there are some areas where newborn screening is not performed. Some regions and countries do not have a public health policy. There is still lots to be done to have newborn screening as a global initiative.

Sean Sanders (host):

Monica, let me come to you with this

next question. I want to get on to the importance of testing. We have touched on the fact that it can identify certain diseases early that can allow early treatment, but maybe you could expand on that and talk about how many disorders are currently screened for. I know it is different in different countries as we just talked about, but if generally, how many disorders are we looking at currently?

Monica Hsiung Wojcik:

I think, just to give you an insight into what happens in the neonatal intensive care unit, for example, I think it is important to highlight differences in terms of trying to identify babies that are asymptomatic or pre-symptomatic for conditions. Jim discussed severe combined immunodeficiency, and Melissa brought up PKU, and both talked about PKU. These are babies that are at risk for severe complications; with insight into the condition they have, you can then, in many cases, offer life-saving treatments.

In the NICU [Neonatal intensive Care Unit], many babies are already sick, and so we have already progressed in that case, beyond the screening panel into the realm of neonatal diagnosis, where we are then trying to use some of the techniques like DNA based sequencing tests to figure out what the baby has once, they are already sick. In contrast the newborn screening panel, which in most cases has, depending on the state, includes dozens of conditions that are supposed to be early onset, treatable and sometimes curable. When we have a baby who's already sick and we are trying to identify the diagnosis, it may be treatable or it may not, and so the way we approach the testing and how we use it might differ than the screening tests that have been talked about before.

Sean Sanders (host):

We are currently not doing genomic screening on newborns as a standard screen, right? This is a different type of test.

Monica Hsiung Wojcik:

Correct, and so the traditional newborn screen is not a genomic screen, meaning it is not generally designed to sequence all the DNA and look for disease causing changes that produce the conditions in question, although there have been some important studies looking into what

that would look like, but right now, there is biochemical tests and other kinds of functional tests, and like I said, it reflects a little bit of the different purpose between a screening and a diagnostic test.

Sean Sanders (host):

Why not screen for more disorders? My understanding is there is about 7000 rare diseases — why not screen for all of them?

Jim Bonham:

It is a good question. At the minute in newborn screening, we depend largely upon biochemical tests, and so first, we have got to have a test, and not all the 7000 rare disorders have a good biochemical marker that we could use for screening. There is a more philosophical reason as well. As someone once said; all screening does harm, some screening does more good than harm, and some of that at reasonable cost, and so there is always a judgment to be made because we are reaching out to families who believe their children to be well, and of course, the reason that most parents look for screening for their children is not necessarily to find out if there is something wrong, but to be reassured that their child who they believe to be well, is in fact well, so any screening result comes as a shock. It is important to balance the potential benefits of identifying children early from the harm that we might do if we over-diagnose or over-treat children.

“We have got to have a test that is highly targeted that does not upset families, we have got to be able to present families with good information to make decisions on.”

Thus, we have got to have a test that is highly targeted that does not upset families, we have got to be able to present families with good information to make decisions on. We have got to be able to offer this test, not just as an isolated test, but as a part of a whole program of care. If the shock comes and the family get a phone call to say that they have got a positive result for their child, then they are immediately plugged in to a responsive and well-organized treatment system, and, that is not always available.

“If the shock comes and the family get a phone call to say that they have got a positive result for their child, then they are immediately plugged in to a responsive and well-organized treatment system.”

When health policy makers begin to decide which conditions they will screen for, they use a set of criteria, and thankfully, there is a set of criteria that has been around for some time, in fact, more or less from the beginning of newborn screening from 1968 called the Wilson and Jungner criteria. The Wilson and Jungner criteria are used to help assess whether or not it is wise in healthcare to screen for a particular condition, and they include criteria like: is this an important condition? Is it treatable? Is it while being rare still common enough to justify a whole population screening program? Is it going to be a proportionate health intervention?

We all end up with different answers because different people make those assessments about the balance of risk and benefit, and sometimes they are public health people, that is people that take an overall view of the good for the population, and sometimes they are influenced by individual clinicians who may lobby for a particular disease that they have seen have devastating consequences for individual children. That difference of approach will often come to differences in decision.

Some of those decision-making bodies ask for published evidence. As we know in rare disease, getting good, published evidence is difficult. If you demand evidence-based published literature before you intervene -- before you start a screening program -- then you will be a little bit behind those who are willing to base recommendations on input from clinicians.

Lastly, some administrations, particularly those that operate socialized medicine, look for detailed explanations for the cost-effectiveness of screening; for example, is this something that we should spend money on, when perhaps we could be spending money on something else? You can imagine in some low- and middle-income countries, there are really difficult decisions about where it is wise to spend your money and get the best outcome for the population that you are responsible for. Taking all of that together, that explains why you get these differenc-

es in choice, ranging in some places from screening for 50 conditions and in other places one or two, or maybe even none at all.

Roberto Giugliani:

You mentioned that there are around 7,000 genetic diseases, why not screen for all of these diseases as well? Jim just pointed out that the condition should have a treatment, should be treatable. So, this limits the number much less than 7,000, in fact just a fraction of that. Also, early diagnosis and early treatment should make a difference to the patient's life. So this further decreases the number of target conditions. Diagnosis is the easiest part of the newborn screening; however, with therapy and the follow up there are a lot of challenges that greatly limit the number of diseases you include in the screening program.

The final number of potentially screened diseases is much lower, around 50, 60, in the most expanded program. Technically, it would be possible to do much more, but you must take these factors into account.

“The focus has always been on screening for disorders that benefit the baby. There must be something for that child that is going to change the outcome of their health, that we can treat, that we can do things for.”

Melissa P. Wasserstein:

We have always used the Wilson and Jungner criteria to guide us about what is appropriate. The focus has always been on screening for disorders that benefit the baby. There must be something for that child that is going to change the outcome of their health, that we can treat, that we can do things for. Now, we can screen for many of these 7,000 rare disorders, and probably have the technology to do so. Is it time for us to rethink those criteria and that definition of benefit? Should newborn screening still just be for the benefit of that baby?

Is it time for us to rethink those [screening] criteria and that definition of benefit?

Should we make sure that there is always a treatment, or can we also think outside the box a little bit? Is there a benefit to the family? Even if we don't have a treatment for that baby, but if that family now knows that God forbid, there is a terrible disorder running in their family, maybe they could use that information to help for genetic counseling for the rest of the family. Is there a benefit to knowing that there is a disorder that might not present until adolescence or adulthood? Is there some benefit to that individual? So, I think it is time for us to start rethinking how we are looking at it, because we are at that stage where we probably can test for all these things.

"Is there a benefit to knowing that there is a disorder that might not present until adolescence or adulthood?"

There are two main facets that we have been discussing. One is: can we do it? Can we look for all these 7,000 disorders? Many of these conditions are defined biochemically and genetically, meaning you might see a biochemical change, or you might find it by a DNA change. We can all think of cases where the traditional newborn screen might have missed a biochemical case that was then detected by a DNA-based test or vice versa. It is still not clear how to best use those two types of testing together to detect all the important conditions.

Monica Hsiung Wojcik:

I think the issues that Melissa was just touching on are critical to consider. She raises some important questions about what is important for the family to know. We use very broad genetic testing like exome and genome sequencing to diagnose infants in the NICU, many of whom may present with something that is relatively localized, like a congenital heart defect, and then we find out the child actually has multi-system disorder that has much more profound implications for things like growth development, intellectual disability and only then we can try to predict what the child's adult life might look like.

We are giving this information to families in certain scenarios that they were not expecting. We must think about how to do that appropriately for these new families. It is really a critical question.

Jim Bonham:

There are two distinct schools of thought. It is probably fair to say that in Europe, we would take a much more guarded view about treating conditions that would be considered not to be treatable. There are several reasons for that; not least, that you take away sometimes what is described as the golden years of having what, to all intents and purposes is a normal child and allowing that bonding to happen with the family. Some families who are given a treatment, a diagnosis for an untreatable condition say that they welcome that early because it cuts down the terrible journey that they go through, getting that information.

It allows them to plan and that is a view that is to be respected. Other parents disagree; the illness has robbed them of an enjoyable childhood with this child, who then subsequently begins to perhaps regress and they feel that they have permanently lost those years and that is been taken away from them. Who has the right to do that?

The other difficulty with spreading the net wider and screening, particularly into conditions where the child does not necessarily become ill until adolescence, is that you remove the right not to know. These babies that are being tested, are being tested without their consent or knowledge, and you are giving them information that is directly relevant to their lives as they grow up, and they have got no choice about that. They simply inherit that, because of a choice for their parents.

There are some real debates to be had and this is going to become, perhaps even more topical as we begin to use that tiny drop of blood. We have the potential to use the tiny drop of blood on filter paper potentially to perform home genome sequencing, and then we get into these very difficult areas for what is it like to have your life mapped out in front of you without your consent and who has the right to do that? These are tricky issues.

"What is it like to have your life mapped out in front of you without your consent and who has the right to do that?"

Sean Sanders (host):

It certainly is a very complex problem to resolve, but I thank you all for your input. I think this is an interesting

discussion and part of the rare diseases issue. I did want to come back to something that we touched on; is testing dangerous and what are the risks, what are the disadvantages?

Jim Bonham:

When you test someone, when you take a blood sample, you give them a little bit of anxiety. You potentially medicalize them, and of course that is not a bad thing if the product is some useful information which can prevent or treat disease. It is a bad thing if you medicalize them and it is just a false alarm -- that does happen, and it happens with screening.

In the screening world this is described as the 'positive predictive value' of the test: if you get a screening test which proves positive, what are the chances from that result that your child really has the condition? In some situations, a positive screening result, means the child has a 90% chance of having that condition for others it can be as low as 5% or 10% or sometimes even less than that.

A false positive screening result is where a child has a positive test but no disease. Studies show that for some people that impact comes and goes, and they get on with their lives. However, for others, that experience results in long-lasting parental stress, and increased use of hospitals, and primary care physicians. In addition, it disturbs normal family life, and that can be comparatively serious for some families. Testing is not an intervention without cost.

"Another thing that we find when we screen for a disease, is that we identify forms of a disease which are much, much milder and possibly would remain asymptomatic right into late childhood or even adulthood."

Another thing that we find when we screen for a disease, is that we identify forms of a disease which are much, much milder and possibly would remain asymptomatic right into late childhood or even adulthood, or perhaps never come to clinical attention. In that sense, we medicalize people, give them a life-long diagnosis, which for them individually is not necessarily justified.

Most screening programs will screen for

congenital hypothyroidism. When we began to screen for congenital hypothyroidism, it was a disorder that happened and around about 1 in 6000 babies, and it happened with twice as many girls being affected as boys. Now, after screening, we identified about 1 in 1500 children, and there are an equal number of girls and boys, and what that is telling us is that whatever we thought we were screening for, it is not the same thing as the clinical condition. Screening changed the goal posts. It may not be wrong, and it may benefit those extra children that have been diagnosed, but it is not exactly the same condition as we were identifying before.

So, there are things still to learn and we sometimes still get it wrong and when we get it wrong, we upset families.

Melissa P. Wasserstein:

Jim raised some excellent points, especially about the uncertainty for some of the disorders on our currently broad screening panels. I think he talked about congenital adrenal hyperplasia, congenital hypothyroidism. We are often finding children who are at risk for later onset conditions and sometimes, we really cannot give a lot of precise information to parents about what to expect, when to expect it, what are the first things to look out for.

It is important to measure what those families are going through: is it a harmful? How severe is it? What are they suffering from? How enduring is it or is it okay? It might be beneficial to find out that information earlier because we will be avoiding the diagnostic odyssey. There is a lot to be studied. We need real data about the potential benefits and potential harms of newborn screening. There is a lot of anecdotal information, a lot of opinions, going for decades, but it is time to now quantify this.

Before the baby is born: “Prenatal testing, including screening and diagnostic tests, can provide valuable information about your baby’s health. Understand the risks and benefits.”

<https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-testing/art-20045177>

Once a baby is born: neonatal screening: “This blood test detects certain rare genetic conditions and metabolic disorders. Screening aims to improve the health of babies by identifying those at risk of developing a serious condition, allowing early intervention.

<https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/new-born-bloodspot-screening>

Roberto Giugliani:

Another thing to be considered is screening the couple before the woman gets pregnant. This called, pre-conceptional screening. There is in place pre-conceptional screening in some communities, mainly where there is higher prevalence of genetic disease. You screen to check the couple if they are carriers or may have some genetic conditions, so they can have genetic counseling before the conception of a baby. This is something also in placement to some areas of some communities.

Monica Hsiung Wojcik:

Preconception testing was just mentioned, where you can see if the couple is a carrier for something that they are at risk of passing along to a baby. Prenatally we can now, in addition to our traditional methods, screen the blood of a pregnant person for certain biochemical things that could suggest the diagnosis or ultrasound findings. We can now do a test on the blood of the pregnant woman to see if there is evidence from the fetal DNA that they have a chromosomal condition, like Down syndrome.

But, if you really want to confirm the diagnosis, you must do a test like amniocentesis or Chorionic Villus Sampling to get cells from the foetus or placenta to really confirm a true positive test. We can apply the same tests we use postnatally, exome or genome sequencing, in the prenatal period as well.

One of the challenges we have in the US is insurance coverage where this testing is expensive. It is sometimes framed as a test you might do if you are deciding whether to continue a pregnancy. But even for couples with an ongoing pregnancy that are committed to continuing, no matter the diagnosis, from my work in the NICU, the delivery room and the ICU taking care of babies who are born with very serious conditions, any insight that you have into that condition as early as possible, provides not only medical benefit to the team, deciding how to appropriately stabilize the baby in the delivery room, how to take care of them in the NICU, and what are there risks for? But this testing is important for psychosocial benefit to the family, they are making some difficult decisions, in particular if the baby is doing worse than expected. It is kind of amazing how many critical decisions we make with so little insight into

what the baby has. From my standpoint, as a neonatologist and geneticists, seeing couples before they even deliver, I feel like many of the couples would share this view that any information about what the baby has is just so important for informed decision making.

Thus, it is much more than a debate over whether the pregnancy continues or not, it really is going to shift our conversations about care from the NICU potentially, or the delivery room to the prenatal period, and I think that has many benefits. It raises a lot of the risk-benefit questions that the others have brought up too in terms of conditions that might not be as treatable, might not be curable, and how are people are going to receive this information. In my practice, the perinatal period, is open for any sort of discussion about what the diagnosis is for the baby and how you are going to treat it.

Sean Sanders (host):

I am guessing the genetic counseling component is very important in this, that once something is detected, the family can then be counseled on how to deal with the potential disease.

Monica Hsiung Wojcik:

Counseling is critical. I mean in all these situations; I think counseling is very important. I would say one of the challenges that we have prenatally, even more so than in newborns, is that the phenotype or the constellation of symptoms can be very unclear. I think folks have touched on this before: the wide spectrum of disease, that we really hadn’t recognized until this genomic era. We are figuring out that all these people had things that we might not have suspected before.

I think that counseling is important because there is a lot of uncertainty. I think people believe that with genetic testing, because we use the term precision medicine, that it is all going to be very precise and accurate, and we are going to know exactly what to do with it - when in fact, it is not. In some ways, it can introduce more uncertainty.

Sean Sanders (host):

Just to clarify something quickly for our audience and something that I find fascinating, so you can detect DNA from a child and biochemical markers from a child in the blood of the mother, is that correct?

“Cell-free DNA testing... fragments of fetal DNA from the placenta in the maternal blood stream.”

Monica Hsiung Wojcik:

Correct. It is referred to cell-free DNA testing where there are fragments of fetal DNA from the placenta in the maternal blood stream. You can identify potential changes in fetal DNA through a sample from the mother's blood, which is fantastic. Because many pregnant people are reluctant to undergo something like an amnio or a CVS procedure. But it is a screening test. We always say that: it is a screening test, meaning that we have had couples that had a high likelihood of something like Down syndrome or Turner syndrome or some other chromosomal condition, and it turns out that the cell-free DNA blood test gave a false positive, meaning that the fetus and the baby did not have that condition. We have also had false negatives where the couple had a normal Cell-free DNA tests and then had a baby that had something like trisomy 13 or trisomy 18.

It really does tie back to the counseling where the family has to understand that as a screening test, there could be both false positives and false negatives, and so we have to conduct a detailed conversation with couples about the risks and benefits of them proceeding to a potential diagnostic test like an amniocentesis or CVS, in the case of either a positive or a negative screening test.

It depends on the clinical picture. We really try to tailor these conversations very specifically to the families. I think understanding the different beliefs and values of families is very important and informative as we decide what to do. I don't think it is going to be a one-size-fits-all approach.

“Understanding the different beliefs and values of families is very important and informative as we decide what to do. I don't think it is going to be a one-size-fits-all approach.”

Sean Sanders (host):

To change gears a little bit, lets talk about what happens after the testing is done. Something that has come up in the previous webinars that we have done, when we have talked about testing of adults and children, not necessarily infants, is that it is really important to put this information in a place where it is accessible. Since rare diseases by their nature are rare, there are very few people that have them, you need that information, and every little bit of information is critical. Can you talk a little bit about how this data is stored, are there central databases in different countries or is there a global database?

Melissa P. Wasserstein:

In the United States, every state has its own newborn screening program, that differs by state. Some states like New York, for example, can save those dried blood spots for up to 27 years, de-identified. They can be used for quality insurance purposes, they can possibly even be used for some de-identified research purposes if they get approval from all the appropriate ethics committees. It is a good question about where it goes and who can access it, and generally it is probably the most secure data you could ever imagine. People cannot just access and even plow through or look through things up or get into anybody's personal information. But if there are samples that are particularly valuable, for example, we are looking for a new disorder, can we use some samples to see if we can detect it? Then that information might be able to, completely de-identified, be shared with other state newborn screening programs who are also trying to get that study on board or that particular screen on board.

It would be great if there was a more centralized database program where people could share outcome data, we could learn from each other, we could learn what is the best outcome, what it is the best time to start treatment, what is the best test for this disorder. It would be ideal if there were more centralized databases. Unfortunately, right now, it is just a little bit choppy.

Roberto Giugliani:

Unfortunately, there is no global database in this regard. There are several initiatives to put these together; to combine the data arising from different countries, from different states, but there is no global database. There are some countries and

states that are able to store this material, and this has been instrumental for development of new tests, as Melissa said, with all the ethical approvals. This is very important.

The information itself is, of course, is protected by the data privacy regulations and is just available to the family, to the patient, and to the individual. But of course, the overall data from the newborn screening programs are very useful to understand the benefits and to make decisions about the continuity of some screening programs and then, decide whether to further expand that program. But it would be great if we have more global datasets.

“It would be great if we have more global datasets.”

Sean Sanders (host):

Jim, in the UK and Europe, what is the set-up there as far as sharing data, especially with researchers?

Jim Bonham:

Every three years, we have an International Congress of Inborn Errors and Metabolism. This year, it is upcoming in Sydney in November, and one of the topics on the agenda is to look at the use of registries of patients, particularly informing outcomes from newborn screening. There are some initiatives in Europe, there is one particularly for inherited metabolic disorders called U-IMD, and that seeks to draw together different national databases and create them into a coherent European database and that would be discussed at this ICIM meeting later this year.

There are some interesting and exciting new developments about using patient registry data, and it is possible without infringing personal identity data which is always the difficulty about sharing data across state boundaries or across international boundaries. It is possible with artificial intelligence to interrogate databases where they are without necessarily revealing personal identification features.

So, let's say you are looking at all patients. We have mentioned the condition PKU. Let's say we are looking at the likelihood of a child developing a particular clinical feature. If we have separately set up registry databases, then it will be possible to send a questioning tool by artificial intelligence, provided they were interoperable and properly mapped.

To be able to interrogate these databases and to provide that information across a global population without necessarily infringing identification of any named patients. So that is an exciting potential development, particularly as you mentioned Sean, for rare diseases because if rare disease's story tells us anything, it tells us that each individual country cannot do this on their own. These conditions are just too rare, and they are not only rare, but they are heterogeneous, that is, they are different even with patients that have these conditions, they are different from one another. We have got to work together on this. As I've said, there are some exciting things that are coming along to inform that, and I think particularly for newborn screening, the outcome from newborn screening is just beginning to be looked at systematically.

Sean Sanders (host):

Are there issues with public trust of newborn testing or is it widely accepted? And in fact, do parents even know that their newborns are being tested -do you request permission from each parent, or is it just done as a standard procedure in many hospitals?

Monica Hsiung Wojcik:

I think you have the option to opt out if you don't want to participate in newborn screening. Any parent though after they have a baby, if you get the file that tells you all the things that are going to happen, most parents will go through it in detail. As a NICU fellow, I would be occasionally called into a room where a parent was wondering about the newborn screening pamphlet, and I would describe it to them. Most of the time, they would not opt out and then have the default screening. But I would say that there are probably many parents who don't thoroughly know about it, and it is sort of 'no news is good news' scenario where the baby was fine, the test was normal, the pediatrician follows up, everything looks good and the parents never hear it about it again. I think many people are happy with that.

To your point about trust: I think there are families that are maybe a little bit more concerned about potentially finding out information that they do not want to hear, and sometimes there is misunderstanding. I think we have all said that the newborn screen ideally finds conditions that are treatable and would have interventions and something that is actionable: most families would want that. I think the fear of finding a diagnosis you cannot do

anything about is often just related to kind of a misunderstanding of the purpose of newborn screening.

Regarding the discussion about what happens with these samples afterwards; where are they going; who has access; is my baby's DNA stored somewhere that could be hacked or could their privacy could be compromised? These are important questions.

Roberto Giugliani:

I think that when you discuss the research that is done with newborn screening, there have been some issues about trust and people questioning the appropriateness of how these samples are handled. However, as others had said, I think it is also part of our mission as clinicians and scientists to understand these disorders and behave in a responsible way. Hopefully we will find better ways to treat this data appropriately and with all the privacy and security considerations, we can make sure to build public trust.

Sean Sanders (host):

Right. What can parents do to be more proactive about understanding newborn screening? Obviously, parents get certain resources when they are at the hospital, but can they do anything themselves to talk, to learn about methods and implications of newborn and even prenatal screening?

Melissa P. Wasserstein:

There is lots of information out there. I think people don't access this as much as we would like them to, but most states have their own state-based newborn screening program that describes what your baby will be screened for if you live in Indiana or if you live in Hawaii, and that also describes the process for sample storage. It will describe what will happen if the baby has a positive newborn screen. There are also national databases/websites that describe newborn screening in general, and so the information is there, the people in the hospital will know about it, the nurses will know about it, the people taking the baby's collection will know about it, the OB-Gyn will know about it, the pediatrician will know about it, so there is lots of resources to ask about screening.

I wish people talked about this a little more, so it is not a surprise that a small number of tests come back a positive screen. And so, when we call to say it is positive, parents say, "What are you talking about, what newborn screen?" I

wish people were looking into it a little bit more, but again, for most people, this is good news. You don't know it happened because it was normal.

Sean Sanders (host):

Roberto, you've been doing this for 35 years. Do you have any advice for parents who wanted to learn more?

Roberto Giugliani:

One point has already mentioned many times on this seminar, is about heterogeneity. The test is to detect an abnormality which can sometimes mean a very dramatic disease but sometimes the same disease can be attenuated and present later in life. Hence, there needs to be better understanding about the meaning of this result.

The second point is especially in developing countries, we need to provide adequate information about the abnormality.

Sean Sanders (host):

One final question: how do you see the future of newborn screening?

Melissa P. Wasserstein:

Babies at birth will have that same tiny little bit of blood that we were talking about before that two to three millimeter punch will be used for sequencing of the exome, or the genome, and that will be the future.

"Babies at birth will have that same tiny little bit of blood that we were talking about before thatwill be used for sequencing of the exome, or the genome, and that will be the future."

I think we have a lot that we need to do before we get there. There are a lot of steps, there is a lot more information. There is too much uncertainty right now. But those are hurdles that we can overcome with time and with a lot of understanding. For example, what should we share at birth? Should we share genetic information when a person turns 18? Should we share it when they are bringing up children? There are a lot of options if you have screening done at birth.

Roberto Giugliani:

I think that genomic screening is something that we will not be able to avoid; it is something that will just happen. At some point the cost is decreasing, the technical situation is improving; what to do with this information, this is the challenge. This is the future of screening. But of course, we should be very careful about how to understand, and how to deliver this information.

Jim Bonham:

Yeah. I've got to say I am a bit more as diehard biochemical person! But I think there is a marriage between both. The reason that I am a bit more diehard biochemical is of course, that biochemistry is more a reflection of what is going on in the metabolism of the patient. It is one thing to have a genetic change, it is another for that to have some systemic effect in the baby. The biochemical information is telling us that. It is telling us that you have actually got some definably disturbed metabolism.

“Clinical exome sequencing (CES), provides an analysis of all protein-coding sequences in the roughly 21,000 genes in the human genome.”

I think you can marry the two together. We currently do that. In any event very often, in CES screening for a condition like cystic fibrosis, we measure a biochemical marker, and then we go on to refine the information from that by doing some genetic testing, and I think that is a marriage made in heaven. It takes us a little bit closer to what's happening in the baby, and hopefully gives us a bit more useful information.

I think the future will be related to genomic sequencing for detection of rare disease. But... we cannot lose the biochemical. the safest way probably involves some combination.

Monica Hsiung Wojcik:

I think the future will be related to genomic sequencing for detection of rare disease. But I also agree with Jim that we cannot lose the biochemical, and so I think the safest way probably involves some combination. There are critically important questions to address; can we interpret all the variants we are going to find and describe what that means for the family?

Are we going to have a healthcare delivery system that is equitable? How are we going to support these families? Who is going to access this information? How are we going to use it?

It is a very exciting time to be in this field, and I am really looking forward to seeing how it continues to develop over the next several decades. I think that we are going to see a lot more with the genomic sequencing.

Sean Sanders (host):

We are out of time, so we are going to have to end our discussion there. Many thanks to our fantastic panel for generously sharing their knowledge and insights. As I mentioned earlier, this webinar is just the fourth in a yearlong series, so please look out for future events at webinar.sciencemag.org and if you'd like to sign up to receive alerts about upcoming events. Thank you once again to our panel, and to Foundation Ipsen for enabling this conversation through their kind sponsorship.



Journal Club

Article of the month

Rare disease: A call for global action for rare diseases in Africa

<https://rdcu.be/cogXW>

Baynam GS, Groft, S, van der Westhuizen FH et al. (2020) A call for global action for rare diseases in Africa. *Nat Genet* 52: 21–26.

<https://doi.org/10.1038/s41588-019-0552-2>

Background info:

- Each rare diseases has a low prevalence; however, the combined impact is 6–8% of the population – similar to Type 2 diabetes!
- Most persons with rare diseases are children.
- Three quarters of rare diseases have genetic associations.
- Rare diseases are often debilitating; impair physical and mental abilities and shorten life span.

- This article discusses how to expand research and diagnostics within the current global collaborative.

In Africa, specific challenges exist – they include:

1. Genomic research in Africa is coming to terms with ethical issues
2. Genomics literacy is evolving
3. There is need for good governance for genomics and biobanking
4. Patients need to be protected
5. Neonatal screening is often not available
6. Healthcare resources per capita are limited
7. Data storage and protection is a challenge

This picture shows the number of people with genome sequences published and listed in genomics databases per country: <https://www.nature.com/articles/s41588-019-0552-2/figures/1>

History of Science

Rosalind Franklin: Genetics' Unsung Hero
by Florian Delval

Have you ever heard about the Matilda effect? It is defined as a bias preventing the recognition of female scientist's achievements whose work is instead attributed to their male colleagues. This bias was first described in 1870 by suffragist and abolitionist Matilda Joslyn Gage. The term “Matilda effect” was coined in 1993 by science historian Margaret Rossiter. Without a doubt, Rosalind Franklin is one of the most notable cases of this effect. A brilliant British scientist, she was of paramount importance in one of history's greatest scientific discoveries: unearthing DNA's double helix structure. Her name would forever be inseparable from two men: Francis Crick and James Watson. Their discovery could be considered as defining the secret of life. But what was its subsequent impact on the history of science?

Discovering the structure of DNA was fundamental, leading to research and imagining technologies that turned the worlds of science and medicine upside down. Once the structure of this molecule, carrying the life of any organism, was elucidated, this was the starting point which made it pos-

sible to better comprehend life, more efficiently understand the way in which cells are born, live and die, and create biotechnologies. Biotechnologies that allow us to make, for example, insulin or to design diagnostic tests for diseases like Covid-19. By understanding its structure, scientists have learned to manipulate, analyze, modify and shape DNA.

For example, we have all heard the term PCR in recent months. PCR is an acronym for “polymerase chain reaction”, the purpose of which is to detect in a highly precise and specific manner the presence of a gene or a sequence within a sample. To perform this technique, we must break the DNA, i.e. separate its two strands, in order to make two authentic copies. Then we repeat, again and again, around 40 times, thus creating enough identical DNA to analyze. In short, there are tons of examples of methods such as the one used for a PCR test. Each technique is a paving stone that has made it possible to establish a more precise understanding of all living things. And if there is one thing to know, had we not established the knowledge of this precise and elegant structure, it would have been impossible for scientists to sequence our genome, identify rare diseases or cancers, design treatments, or find new forms of vaccines.

What Rosalind Franklin, James Watson or Francis Crick accomplished is nothing short of inventing the wheel without ever having thought of the concept of a car. Research, or progress, is nothing more or less than a succession of brilliant ideas, all thought from a point, which we call “origin”.

Talking about Rosalind Franklin’s history therefore means talking about the great history of DNA. At the time of Rosalind Franklin, very little was known about it. In 1936, Oswald Avery, geneticist at the Rockefeller Institute hypothesized that the transforming agent, the element which carries genetic information from a chromosome to its copy, was possibly DNA. But back then, much of the scientific community still believed that genes were made up of proteins, and did not believe that genetic material could be made of deoxyribonucleic acid. Marked as the century of great advances, the twentieth century could be composed of two eras. Its first half is that of physics with the theory of general relativity, quantum mechanics or nuclear fission. Its second half could be composed of biology. This second half we owe in part to Rosalind Franklin. It was she who, unwittingly, provided essential material needed by those who would subsequently be behind the elucidation of DNA’s double helix structure: Francis Crick and James Watson.

This unintentionally provided material by Rosalind Franklin consisted of two import-

ant things: an incalculable amount of experimental data, and a photo that became iconic: Photo 51. Nowadays, it is possible to find numerous articles and videos on Rosalind Franklin - a simple YouTube search will redirect you to videos that aspire to summarize her story in a few short minutes. Unfortunately, many mistakes and untruths often dot these efforts to provide due credit. It therefore seems critically important from our point of view to describe in detail Rosalind Franklin, who was a fundamental figure to the history of science, and because her work represents something greater than being known historically as the one whose research was plundered. These episodes rely heavily on the book *Rosalind Franklin, The Dark Lady of DNA*, written by journalist Brenda Maddox. If you are interested in Rosalind Franklin’s story, this book is essential. Brenda Maddox, quoted many times throughout the next few episodes, had unique access to Rosalind Franklin’s correspondence with her family and loved ones throughout the course of her life. Maddox also made a remarkable effort to popularize science, and interviewed protagonists of this story on numerous occasions. This book provides a great opportunity to discover the story of Rosalind Franklin through her eyes, especially since for too long, this story has been told only by those who tried to minimize her impact on science and the world.

To learn more about Rosalind Franklin’s story, listen to Fondation Ipsen’s La Science Quelle(s) Histoire(s) - a podcast channel focused on the history of science.

What’s up?

Highlights of the month

Movies to move you by Morgan Packer

Rosalind Franklin was a key pioneer in defining the structure of DNA, outshined by her male counterparts, James Watson and Francis Crick. Her work around DNA was groundbreaking, characterizing its’ density and shape . In retrospect, her noble discovery has been given greater recognition post-mortem through several documentaries and films.

Here are a few of my recommendations highlighting the impressive story of Rosalind Franklin:

1. ***The Race for the Double Helix***: An award-winning documentary produced for BBC’s science series Horizon starring Jeff Goldblum, Tim Piggot-Smith, Alan Howard and Juliet Stevenson, depicting the race to discover DNA’s molecular structure. While this documentary aired in 1987, it can be found easily available for free online.
2. ***Secret of Photo 51***: This documentary, which originally aired in 2003 under NOVA’s Science Programming, used interviews with surviving members of the story to describe how Franklin’s research provided James Watson and Francis Crick with a critically important missing piece of their research puzzle – enabling them to define the structure of DNA and win the Nobel Prize.
3. ***Photograph 51***: A special mention with Nicole Kidman starring as Rosalind Franklin in a London West-End based play. While the play only ran for a limited time in 2015, its two-part audiobook version is still available through LA Theatre Works.

Jonas and Abequa’s flowers

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(in French)

Neonatal testing for rare diseases

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