Clinical Chemistry

Is the $1000 Genome as Near as We Think?

Article: Kirsten J.M. van Nimwegen, et al.
Is the $1000 Genome as Near as We Think?
Clin Chem 2016;62:1458-1464.
http://clinchem.aaccjnls.org/content/62/11/1458

Guest: Kirsten van Nimwegen is a PhD student in Health Technology Assessment of the Radboud Institute of Health Sciences at the Radboud University Medical Center in the Netherlands.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

It is becoming less and less expensive to sequence human DNA. A key milestone in advances within genomic technologies is the availability of the so called $1,000 genome. Important, because experts proposed that this is the point where routine genome sequencing may become feasible.

Commercial parties now have claimed that they've achieved sequencing the human genome for just under $1,000. Though this may be true, there are many complexities associated with this cost estimation. A report in the November 2016 issue of *Clinical Chemistry* evaluates costs associated with next generation sequencing applied for whole genome, whole exome, and targeted gene panel analysis.

The study's primary author is Kirsten van Nimwegen, a PhD student in Health Technology Assessment of the Radboud Institute of Health Sciences at the Radboud University Medical Center in the Netherlands. She researches the cost effectiveness of next generation sequencing techniques with the focus on whole exome sequencing in pediatric neurology, and she joins us for this podcast.

So, you stated in your recently published paper in *Clinical Chemistry*, commercial parties in the field of next generation sequencing often claimed that a human genome can nowadays be sequenced for less than $1,000. So tell us, is this really the case?

Kirsten: Well, over the last years and especially with the introduction of next generation sequencing, the costs for DNA sequencing have dropped enormously. Commercial parties indeed claim now that they are able to sequence the human genome for less than $1,000. In theory, they can do this. However, what they included in this $1,000 are only materials for the sequencing process itself, so the equipment and the consumables and this add up to

approximately $1,200. However, the cost for sequencing, of course not only the total cost for a sample, apart from sequencing, expensive equipment has to be acquired and maintained. Personnel is needed to draw blood, extract the DNA, prepare and run the sample. Also, data interpretation and reporting has to be included. So, taking all these factors into account, we calculated that the actual per sample cost are around 1,700 Euros which is over $1,800. So I think we can say that the acclaimed $1,000 genome is not yet achieved now.

Bob Barrett: Do you think we'll see that $1,000 genome in the near future?

Kirsten: Over the last decades, we saw a tremendous drop in the sequencing costs. Ten years ago, sequencing a million base pairs cost approximately $1,000 and now these costs are already below ten cents. However, it is difficult to predict whether these costs will continue to drop and how far they will go. Therefore, we performed also a sensitivity analysis. In this analysis, we changed the input parameters that influence the cost of genome sequencing so we get an insight into which cost components might contribute to cost reductions in the future, and to what extent these cost reductions might be expected.

So, we determined what the influence is of dropping costs for the equipment, dropping costs for the consumables, but also what happens to the cost with various sequencing depths. For example, of various life cycles. So, we then constructed a best-case scenario analysis to gain insight into the extent to which future cost reductions might realistically be expected under the most optimistic assumptions. The scenario assumed 50% cost reductions in both the equipment and the consumable costs, and a sequencing depth of 30 times, five years life cycles, and very efficient use of the equipment. In this scenario, whole genome sequencing would still cost 1,000 Euros per sample, meaning that $1,000 per sample is not yet achieved.

The main contributors to the costs are the consumable costs. So to reach this $1,000 genome, especially the consumables need to become cheaper. This is only likely to happen if new parties in sequencing technology arise, which results in competition on the market.

Bob Barrett: In your recent study, you compared cost for three approaches using next generation sequencing: whole genome, whole exome, and targeted gene panel sequencing. How do the cost of these tests compare?

Kirsten: With whole genome sequencing, the entire human genome is sequenced. With whole exome sequencing and targeted

gene panel sequencing, you sequence significantly less DNA; hence you would expect that these techniques are a lot less expensive than genome sequencing. Indeed, we did find that these techniques are considerably cheaper. With whole exome sequencing, you look at only the protein-coding regions which are about 1 to 2% of the genome. This region of the genomes, it is believed to hover about 85% of all disease-causing mutations.

Whole exome sequencing can nowadays be done for approximately 800 Euros. This is a suitable approach in heterogeneous diseases with pure knowledge on the genetics underlying the disease. If more is known about genetic mechanisms, one might rather specifically sequence a targeted gene panel, and this can nowadays be done for about 300 Euros. So, these techniques are considerably cheaper alternatives to genome sequencing.

Bob Barrett: So since targeted gene panels and whole exome sequencing are that much cheaper, why would you perform whole genome sequencing?

Kirsten: As I already mentioned, about 85% of all mutations are believed to occur in the protein-coding regions, the exome. So, about 15% cannot be found with whole exome sequencing or targeted gene panels. Moreover, the level of techniques require a so-called library preparation, defining which parts of the DNA are selected for sequencing, and these DNA fragments are then amplified and sequenced. As whole genome sequencing does not require this step, it's better able to detect copy number changes, repeat changes, and small deletions. So in diseases, where these mutations play a role, whole genome sequencing is simply more sensitive than whole exome sequencing.

Bob Barrett: Now if I were a doctor -- that would make my mother very happy but thank goodness I'm not. If I were a doctor and seeing a patient with a suspected genetic disorder, which next generation sequencing test would you recommend I order?

Kirsten: That really depends on the patient that you are seeing. Although exome sequencing and targeted gene panel sequencing are way less costly alternatives to genome sequencing, this does not imply that these approaches should be preferred in clinical practice. The choice of the sequencing approach you use should not only be based on its costs but also of course on its clinical consequences. For example, its diagnostic yield. And whether the diagnostic yields of genome sequencing is higher than diagnostic yields of exome sequencing or targeted gene panels, that really depends on your patient population.

If a lot were already known on the genetic mechanisms behind a certain disease, a targeted gene panel including only those genes that are known to be involved is probably the best choice as it is expected to result in the diagnosis and it is relatively cheap. However, if a patient presents with clinical heterogeneous symptoms which can fit multiple disorders or when less is known about the genetics behind the disease, targeted gene panels are not so likely to find the disease-causing mutations.

In these cases, exome sequencing and genome sequencing might be the more valuable test. And then there's the difference between exome sequencing and genome sequencing and diagnostic yield. Although whole exome sequencing already takes into account, all protein coating regions in which 85% of all mutations are believed to occur, genome sequencing is better able to detect structural variations.

So, if you are seeing a patient who is expected to have a disease in which these kinds of variations play a large role, then genome sequencing might be the better choice, whereas in diseases where structural variants don't play a role, you might rather choose for exome sequencing. So, for each patient population, the decision on which next generation sequencing approach you should use should be based on a careful tradeoff between the cost on the one hand and the consequences on the other hand. And the cost calculations that we perform, of course, contribute at making these tradeoffs as these costs can be used in future cost effectiveness analysis.

Bob Barrett: Finally, since healthcare cost are rising worldwide, cost-effectiveness analysis are becoming more and more important to allocate the scarce resources towards these medical interventions that provide most value for the money. Can your results be directly used as input for future cost-effectiveness analysis?

Kirsten: No. Although our calculated costs are a good indication of the real cost, they cannot be directly used as an input for cost-effectiveness analysis for several reasons. First, our costs are still slight underestimation. We decided to only calculate those costs of the diagnostic test itself. So everything from drawing the blood to data analysis and data reports is included. However, a patient will also have a consult with his physician or with his clinical geneticist before the test is performed but also when the results are reported.

And in a full cost-effectiveness analysis, these costs should also be included. Other costs that's also should be incorporated in a full economic analysis are the downstream

costs for additional testing, medication, or genetic counseling.

And these costs or maybe savings were not taken into account because they're very disease and patient-specific, so we left those out. This is also the case for the overhead costs which are costs for water or electricity, floor space. These vary so much between laboratories that we decided not to take those into account.

Moreover, our cost calculations are based on some assumptions. We calculated the cost for three Illumina platforms which are often used in clinical practice. But of course using a different platform or consumables of different supplier will also result in different per sample cost. Also, we assumed sequencing depth of 30 times, while currently no gold standard exists, so this might differ between laboratories.

Sequencing at different depth will also influence the cost of course. Finally, the cost of personnel were based on their salaries, and this will also differ between countries and should be adapted to laboratory-specific conditions. So, as you can see, our costs cannot be directly used as an input for cost-effectiveness analysis. However, with our recent publication in *Clinical Chemistry*, we also added calculation sheets. In this Excel sheet, cost parameters can be adapted to laboratory specific conditions calculating the laboratory specific costs.

Some cost parameters are directly transferable. First, we made use of the universal list prices of the suppliers of the equipment and consumables. And for cloud computing and storage, we used Amazon prices. So if using the same sequencing platform and the same consumables, the costs we calculated are partly directly transferable.

Bob Barrett: Kirsten van Nimwegen is a PhD student in Health Technology Assessment of the Radboud Institute of Health Sciences at the Radboud University Medical Center in the Netherlands. She's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.