Clinical Chemistry 62:11
1458–1464 (2016)

Is the $1000 Genome as Near as We Think? A Cost Analysis of Next-Generation Sequencing

Kirsten J.M. van Nimwegen,[1*] Ronald A. van Soest,[2] Joris A. Veltman,[2,3] Marcel R. Nelen,[2] Gert Jan van der Wilt,[4] Lisenka E.L.M. Vissers,[2] and Janneke P.C. Grutters[1]

BACKGROUND: The substantial technological advancements in next-generation sequencing (NGS), combined with dropping costs, have allowed for a swift diffusion of NGS applications in clinical settings. Although several commercial parties report to have broken the $1000 barrier for sequencing an entire human genome, a valid cost overview for NGS is currently lacking. This study provides a complete, transparent and up-to-date overview of the total costs of different NGS applications.

METHODS: Cost calculations for targeted gene panels (TGP), whole exome sequencing (WES) and whole genome sequencing (WGS) were based on the Illumina NextSeq500, HiSeq4000, and HiSeqX5 platforms, respectively. To anticipate future developments, sensitivity analyses are performed.

RESULTS: Per-sample costs were €1669 for WGS, € 792 for WES and €333 for TGP. To reach the coveted $1000 genome, not only is the long-term and efficient use of the sequencing equipment needed, but also large reductions in capital costs and especially consumable costs are also required.

CONCLUSIONS: WES and TGP are considerably lower-cost alternatives to WGS. However, this does not imply that these NGS approaches should be preferred in clinical practice, since this should be based on the tradeoff between costs and the expected clinical utility of the approach chosen. The results of the present study contribute to the evaluation of such tradeoffs.

Over the last years, substantial technological advancements in next-generation sequencing (NGS)[5] have been made in terms of sequencing speed, read length, and throughput *(1)*. At the same time, sequencing costs have rapidly decreased, contributing to a rapid diffusion of NGS applications into clinical settings *(2–4)*. Whereas only 10 years ago the sequencing costs of a million base pairs were approximately $1000, the costs are now below $0.10 *(2, 5–8)*. Several commercial parties claim to have broken the barrier of the $1000 genome *(9, 10)*, an accomplishment that would allow for large-scale clinical application, furthering our understanding of genetic diseases and ultimately contributing to personalized medicine in a major way *(11)*.

In clinical applications, 3 NGS approaches are predominantly applied in postnatal settings: targeted gene panels (TGP), whole-exome sequencing (WES), and whole-genome sequencing (WGS). These techniques have not only proven to be promising tools in studying the genetics underlying rare Mendelian disorders *(12–14)*, but have also been shown to be valuable diagnostic tools in genetic diseases *(3, 8, 15–19)*. A recent review showed that although several studies on the cost-effectiveness of NGS applications have been performed, a complete and valid cost overview is currently lacking *(20)*. Moreover, the costs for the sequencing process itself might be only a small part of the total costs. Apart from sequencing, expensive equipment must be acquired and maintained; personnel are needed for sample preparation, data interpretation, and reports; and large amounts of data must be managed and properly stored. Because these costs are often not taken into account, the real costs of NGS applications are often considerably underestimated. It

[1] Department for Health Evidence, Radboud Institute for Health Sciences, Radboud university medical center; [2] Department of Human Genetics, Donders Centre for Neuroscience, and [4] Department for Health Evidence, Donders Centre for Neuroscience, Radboud university medical center, Nijmegen, the Netherlands; [3] Department of Clinical Genetics, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands.

* Address correspondence to this author at: Radboud university medical center, Department for Health Evidence, Geert Grooteplein Noord 21, Mailbox 133, Nijmegen, 6525EZ the Netherlands. Fax +31-(0)24-3613505; e-mail kirsten.vannimwegen@radboudumc.nl.

Received April 7, 2016; accepted July 19, 2016.
Previously published online at DOI: 10.1373/clinchem.2016.258632

[5] Nonstandard abbreviations: NGS, next-generation sequencing; TGP, targeted gene panel; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Table 1. Base case assumptions for cost calculations of NGS applications.

	TGP	WES	WGS
Sequencing platform	NextSeq500	HiSeq4000	HiSeqX5
Life cycle of the platform, years	5	5	5
Average coverage	100×	70×	30×
Capacity, samples per year[a]	248 927	7800	9801
Utilization	10%	75%	75%
Actual annual throughput	24 892	5850	7350
Data processing, CPU h per sample	5	100	1000
Data storage, GB per sample	1	150	600
Data storage time	5 years	5 years	5 years
Personnel sample preparation[b]	10 000 samples per FTE	1280 samples per FTE	1280 samples per FTE
Personnel first data analysis [b]	10 000 samples per FTE	1280 samples per FTE	1280 samples per FTE
Personnel for data interpretation and report[c]	30 min per sample	60 min per sample	90 min per sample
Software for read mapping, variant calling, and annotation	Freeware[d]	Freeware[d]	Freeware[d]

[a] For TGP a gene panel consisting of 90 genes, with a mean of 23 amplicons per gene, is assumed.
[b] One FTE represents a gross annual salary of €32,268, which is the average gross salary of a laboratory technician in the Netherlands.
[c] Data interpretation is done by a clinical molecular geneticist with a gross annual salary of €69,408.
[d] For example, Burrows-Wheeler Aligner (BWA), Genome Analysis Toolkit (GATK), and Variant Effect Predictor (VEP) for TGP, WES, and WGS.

is therefore questionable whether the $1000 genome has indeed been achieved or is within reach in the near future.

This study aimed to answer this question by providing a complete and transparent overview of the total per-sample costs of the clinical application of TGP, WES, and WGS, which could serve as a resource for future cost-effectiveness analyses and inform clinical decision makers on which NGS approach to use.

Methods

AVAILABILITY OF DATA

All data used for the study are available in the online Supplemental Materials file that accompanies the online version of this article at http://www.clinchem.org/content/vol62/issue11.

FRAMEWORK FOR COST CALCULATION

Relevant cost items and associated prices were determined in the Radboud university medical center. Our calculations were based on platforms that are currently used in clinical practice: the NextSeq500 (TGP), HiSeq4000 (WES), and HiSeqX5 (WGS). All 3 platforms were from Illumina. We assumed that the genetic material was obtained from whole blood via venipuncture. Base case assumptions on sequencing platforms, technical details, and personnel are shown in Table 1.

Since per-sample costs of NGS could be influenced by the selected sequencing platform, consumables, and instrument/platform utilization, a costing model was developed in Microsoft Excel, in which all cost components were incorporated and could be adapted to laboratory-specific conditions (see the online Supplemental Materials file).

Sequencing depth was arbitrarily chosen to resemble current clinical practice at the Radboud university medical center and other diagnostic laboratories *(21–24)*. Sequencing depths of 100×, 70×, and 30× were assumed for TGP, WES, and WGS, respectively.

Utilization of the platforms of 75% was assumed for WES and WGS since 100% utilization is unlikely to be due to contributing factors such as maintenance. For TGP a utilization of only 10% was assumed since the capacity of the machine substantially exceeded demand and realistic clinical throughput.

Personnel time required for sample preparation, sequencing, data analysis, and interpretation were based on in-house experience for TGP and WES and were extrapolated for WGS.

BREAKDOWN OF COSTS

Costs were divided into three categories: capital costs, maintenance costs, and operational costs. Capital costs were defined as the nonrecurring costs for equipment, consisting of the platform itself and, in case of WES and

WGS, the Hamilton Microlab STARlet, which was required for sample preparation. Yearly capital costs were calculated by dividing the initial costs for equipment acquisition by an annuity factor, taking into account the lifetime of the equipment (5 years), and an interest rate of 4.5%, as advised in the *Dutch Manual for Costing: Methods and Reference Prices for Economic Evaluations in Healthcare (25)*.

Maintenance costs were defined as the yearly costs for maintaining the equipment, and were fixed in agreement with the manufacturer. During the first year, no maintenance costs were calculated since these costs are generally included in the initial acquisition costs. Platform-related unit prices, such as acquisition, maintenance and consumables were based on list prices of the supplier to enhance transparency and transferability of the results between hospitals and countries. Other costs, such as personnel, were derived from the hospital's financial administration.

Operational costs were defined as the costs for running the sample, and included consumables, personnel, data handling, processing, interpretation and storage. The operational per-sample costs were added to the per-sample capital and maintenance costs, resulting in a total per-sample cost.

Only direct costs associated with NGS were taken into account. Indirect costs, such as clinical geneticist consultations, downstream costs for additional testing and treatment, and overhead costs, were not taken into account. All costs are expressed in 2015 euros. A detailed overview of the assumptions underlying our calculations is provided in the online Supplemental Materials file.

ANALYSES

In the base case analysis, we calculated the per-sample capital, maintenance and operational costs for all three approaches using the assumptions as described in Table 1.

Considerable technical advances in NGS applications have been made in recent years. Simultaneously, the costs have rapidly decreased and have deviated from Moore's law *(6)*. Although it is difficult to predict whether costs will continue to drop, scenario and sensitivity analyses provide insight into which cost components might contribute to future cost reductions, and to what extent these costs reductions might be expected. Sensitivity analyses are analyses that show how the per-sample costs are influenced by the changes in the various input parameters, e.g., coverage, utilization and life cycle of the equipment and capital or consumables costs *(26)*. To this end, we varied the main parameters of the base case analysis.

To determine the influence of the investment costs for equipment on the per-sample costs, a sensitivity analysis was performed in which the capital costs for the sequencing platform were reduced by 50%. This was also done for the costs of consumables.

Because technical developments are expected to continue, the life cycle of 5 years used in the base case calculations might be an overestimation. Therefore, the life cycle of the NGS platforms was varied between 3 and 5 years.

Additionally, since there is currently no gold standard for sequencing depth in clinical applications, coverage varied between 30× and 100×. Utilization varied between 1% and 15% for TGP and between 55% and 95% for WES and WGS. Finally, to indicate to what extent future cost reductions might be expected, a best-case and worst-case scenario were constructed, providing a lower and upper bound of the expected costs of NGS in the near future.

Results

COST ANALYSIS

Annual capital costs for WGS (€1.3 million) were 6 and 27 times as high as the capital costs for WES (€205 847) and TGP (€47 074), respectively (Table 2). Given the assumed platform utilization and coverage, per-sample capital costs were €175 (WGS), €35 (WES), and €2 (TGP). Per-sample maintenance costs of WGS were €72, which was 6 and 79 times higher than for WES (€12) and TGP (€1), respectively. The operational costs accounted for the largest part of the per-sample costs of NGS applications, adding up to €330 for TGP, €744 for WES, and €1422 for WGS, with the major cost drivers being the consumables required for sample preparation and sequencing.

Under the assumptions shown in Table 1, total per-sample costs of TGP, WES, and WGS, were €333, €792, and €1669, respectively. Table 2 displays an overview of the costs of the NGS applications, with a detailed outlining available in the online Supplemental Materials file.

SENSITIVITY ANALYSES

Capital costs accounted for only a small percentage of the per-sample costs (0.6%, 4.4%, and 10.5% for TGP, WES and WGS, respectively). Future reductions of 50% in these capital costs therefore would have only a modest impact on the per-sample costs, reducing the per-sample costs of TGP, WES and WGS by 0.3%, 2.1%, and 5.2%, respectively (Table 3). Reducing the consumable costs for enrichment and sequencing by 50%, on the other hand, decreased the per-sample costs of TGP, WES, and WGS by 37.1%, 35.2%, and 32.5%, respectively.

Decreasing the life cycles of the platforms from 5 years to 3 years had a modest impact, increasing the per-sample costs of TGP, WES, and WGS by 0.3%, 2.3%, and 5.5% respectively.

Varying the sequencing depth between 30× and 100× coverage had a modest impact on the per-sample

Table 2. Costs (euros per sample) of the NGS applications, based on the base case assumptions.

	TGP	WES	WGS
Sequencing platform	NextSeq500	HiSeq4000	HiSeqX5
Annual throughput (utilization)	24 892 (10%)	5850 (75%)	7350 (75%)
Capital costs			
Platform initial costs	206 654.00	853 738.00	5 607 475.00
Hamilton Microlab STARlet	0.00	90 000.00	90 000.00
Capital costs per year[a]	47 073.80	205 847.04	1 288 702.85
Capital costs per sample	1.89	35.19	175.33
Maintenance			
Annual maintenance contract with Illumina[b]	28 300.00	83 000.00	655 000.00
Annual maintenance contract Hamilton Microlab STARlet	0.00	5509.00	5509.00
Maintenance costs per year	22 640.00	71 909.00	529 509.00
Maintenance costs per sample	0.91	12.29	72.04
Operational costs per sample			
Blood withdrawal	10.64	10.64	10.64
DNA extraction	31.53	31.53	31.53
Sample preparation consumables	242.62	296.68	27.61
Sequencing consumables	4.56	262.24	1057.81
Lab personnel	8.97	70.08	70.08
Data processing[c]	0.50	10.00	100.00
Data storage[c]	0.05	0.75	30.00
Data interpretation and report	31.23	62.65	93.97
Operational costs per sample	330.10	744.27	1421.64
Total costs per sample	332.90	791.75	1669.02

[a] To calculate the annual capital costs, the platform initial costs were divided by 4.39, and the costs for the Hamilton Microlab STARlet were divided by 7.913. These annuity factors take into account a life cycle of 5 and 10 years, respectively, and an interest rate of 4.5% [Tan et al. *(25)*].
[b] During the first year of the life cycle no maintenance costs occur since these are included in the initial price of the equipment.
[c] Costs for data processing and data storage are estimated on €0.10 per CPU hours and €0.01 per GB, based on the commercial pricing of Amazon for cloud computing and data storage. It is assumed that data is stored for 5 years [Amazon *(35)*].

costs of TGP, while it influenced per-sample costs of WGS considerably. Costs varied between €328 and €333 (TGP), €615 and €929 (WES), and €1669 and €5430 (WGS). Varying the platform utilization rate resulted in per-sample costs between €332 and €358 (TGP), €782 and €809 (WES), and €1617 and €1759 (WGS). An overview of the sensitivity analyses is displayed in Table 3.

BEST-CASE AND WORST-CASE SCENARIO ANALYSES

To gain insight into the extent to which future cost reductions might realistically be expected, best-case and worst-case scenarios were constructed (Table 4).

In the most optimistic scenario, per-sample costs could be reduced by 38.3%, 49.3%, and 39.8%, to €205 (TGP), €401 (WES), and €1006 (WGS), respectively. This scenario required very efficient and long-term application of the sequencing equipment, cost reductions of 50% in both capital and consumable costs, and technological advances allowing for 30× coverage. On the other hand, short-term and inefficient use of the sequencing equipment, in combination with a sequencing depth of 100×, might increase the per-sample costs by 10.5%, 24.9%, and 268.9% for TGP, WES, and WGS, respectively.

Discussion

In this study we attempted to provide a transparent, complete and up-to-date overview of the costs of diagnostic NGS applications, including not only the sequencing process but also equipment acquisition and maintenance and data analysis and storage. With estimated per-sample costs of €1669 for WGS, the desirable $1000 genome has not yet been achieved. In the best-case scenario for anticipated future cost developments, however, the per-

Table 3. Sensitivity analyses.

	Per-sample costs, €		
	TGP	WES	WGS
Base case	333	792	1669
Capital costs −50%	332	775	1582
Consumable costs −50%	209	513	1126
Life cycles of 3 years	334	810	1761
30× coverage	328	615	1669
100× coverage	333	929	5430
Lower utilization (1%, 55%, 55%)	358	809	1759
Higher utilization (15%, 95%, 95%)	332	782	617

sample costs of WGS approach €1000, which is nowadays approximately $1100 *(27)*.

Per-sample costs for TGP (€333) and WES (€792) were considerably lower. The large differences in per-sample costs are mainly caused by the consumables for sample preparation and sequencing, which are the major cost driver. For TGP these costs add up to €247, for WES to €559, and for WGS these are €1085. These differences are caused by the large differences in the number of bases sequenced, affecting both consumable price and annual throughput of the NGS systems. Whereas with WGS the entire genome is sequenced, WES sequences only the protein-coding parts (exons), which constitute approximately 1%–2% of the genome *(8, 20, 28)*. The sensitivity analyses showed that future cost reductions are most likely to occur if consumable costs decrease considerably. Currently, a few large players dominate the sequencing market. Therefore, it is questionable whether the costs for consumables and equipment will decrease further, or might even increase as a result of these monopoly positions.

However, with the increased application of NGS in clinical settings it is likely that new parties in sequencing technology will arise. As a result of competition and economies of scale, this might result in cost reductions for both equipment and consumables.

Recently, another microcosting analysis reported considerably higher per-sample costs for TGP (€589–€1949) and WES (€499–3388) *(29)*. These costs are not directly comparable to our cost calculations since they provide mean costs based on the cost analyses of 9 different laboratories involving various sequencing platforms and consumables, applied in both germline and somatic mutations. Life cycles and sequencing depth were not specified and might even differ between laboratories. Moreover, their calculations included confirmative testing, development and validation of the bioinformatics pipeline and protocols, and overhead costs, which we did not include.

The main strength of our study is the transparency and transferability of our cost calculations. Although the per-sample costs found in this study are not directly generalizable, by specifically stating which costs are included, which are not, and how we valued every cost category, we ensured transparent results. The use of universal list prices and current Amazon prices for cloud computing and storage allows for direct transferability of the capital, maintenance, and consumable costs, and data processing and storage costs within and between countries. Choosing other methods of data processing and storage will bring along additional costs for hardware and software. Other costs that will differ between laboratories and should be adapted (shown in the Excel sheet provided in the online Supplemental file) are costs for personnel and costs if other platforms or consumables are used. Additionally, costs will vary with sequencing depth and chosen software for read mapping, variant calling, and annotation. Note that overhead costs are not incorporated in our cost calculations and will also differ considerably between laboratories.

The provision of a calculation sheet (see the online Supplemental Materials file) allows for easy adjustment of the costs to specific situations. Therefore, our results could be very useful, both in clinical decision-making

Table 4. Best-case and worst-case scenario analyses.

	Best case			Worst case		
	TGP	WES	WGS	TGP	WES	WGS
Capital costs	−50%	−50%	−50%	Current	Current	Current
Consumable costs	−50%	−50%	−50%	Current	Current	Current
Life cycle, years	5	5	5	3	3	3
Utilization	15%	95%	95%	1%	55%	55%
Required coverage	30×	30×	30×	100×	100×	100×
Per-sample costs, €	205	401	006	368	989	6157

and as input for future cost-effectiveness analyses. One should keep in mind that we calculated the direct costs for diagnostic applications of NGS from a hospital perspective. For a full health economic analysis, a societal perspective should be adopted that also considers patient costs.

Despite these strengths, this study has a number of limitations. First, per-sample costs of these technologies depend on the sequencing platform used. In our study we calculated the per-sample costs based on 3 Illumina platforms because they currently are the market leader in sequencing technology. However, a large diversity of suppliers and platforms is available.

Second, several platforms allow for multiple applications. The Illumina HiSeq4000, for example, can be used both for WES and WGS. One could argue that for smaller sequencing centers, it might be more efficient to offer 1 or 2 sequencing technologies, and buy only 1 platform on which all analyses can be performed. For sequencing centers with a large annual throughput it might be more cost-effective to offer all technologies and buy 3 different platforms with a capacity as high as possible. However, the aim of this study was to provide a complete and transparent overview of the per-sample costs of the clinical application of TGP, WES, and WGS. Deciding which (combination of) sequencing platforms a specific sequencing center should use given its expected annual throughput is beyond the scope of this report. Nonetheless, the calculation sheet in the online Supplemental Materials file allows for easy adjustment of all costs to laboratory-specific situations, and can therefore be used as a useful tool for (clinical) decision-making regarding sequencing equipment and respective running costs.

Third, per-sample costs as calculated in this study are still a slight underestimation of the real per-sample costs. As Buchanan et al. stress, costs such as those for the clinical geneticist consult for reporting the results to the patient should also be included *(30)*. These were not taken into account in our calculations because we aimed to provide per-sample costs for the diagnostic test only. Importantly, there is little to no experience in the large-scale use of genome sequencing in clinical practice, making it hard to estimate personnel costs for interpretation. Interpretation is much easier in the coding region than in the noncoding region, and diagnostic interpretation of genomes may initially remain limited to variants affecting the coding region. For this reason we have not increased interpretation time extensively in our cost calculations. Also, the overhead costs were not taken into account because these were expected to vary considerably between, and even within, countries. Other costs that contribute to the per-sample costs of NGS applications are downstream costs such as additional testing, medication, or genetic counseling resulting from NGS. Notably, whereas the cost of WGS may initially be higher, it may result in a reluctance to use future genetic diagnostic testing, thereby possibly reducing costs in the long term. These costs and/or savings were not taken into account because they were expected to vary considerably between patient populations. For a full health economic evaluation however, they should be incorporated.

Finally, in current clinical practice, no gold standard for sequencing depth exists. Commercial parties have recommended 30× coverage for WGS for the detection of germline mutations. Although this has not yet been evaluated for clinical applications, a recent study has shown that, for germline mutation detection, a lower coverage is required for WGS than for WES because WGS does not involve an enrichment step and therefore minimizes coverage variation over the sequencing targets *(21)*. However, other studies have shown that, in clinical settings, a higher coverage may be required for accurate mutation calling, especially when considering the detection of low-level somatic mutations that are increasingly being recognized as a prominent cause of genetic disease *(31–33)*. A higher coverage, and thereby higher quality, however, inevitably go with higher per-sample costs because every base is sequenced more times. Although our cost calculations assumed germline mutations, the provided calculation sheet allows for cost calculation for adjusted coverage in somatic, infectious disease, or microbiological applications.

WES and TGP are considerably less costly alternatives compared to WGS for genetic diagnostics in clinical practice. However, this does not imply that these should be preferred in clinical practice because the choice of NGS approach depends not only on the per-sample costs but also on its diagnostic yield, which defines its effectiveness. It also depends on how many patients require additional diagnostic testing. Moreover, a genetic diagnosis might alter treatment, and thereby improve health-related quality of life. Whether the diagnostic yield of WGS will be considerably higher than the yield of TGP depends on the patient population. Also, comparing WGS to WES might result in small differences in diagnostic yield since WES already takes into account all protein-coding regions, in which 85% of all mutations are believed to occur *(34)*. On the other hand, WGS is able to better detect copy-number changes, triplet repeat changes, and small deletions than WES and might therefore have a higher diagnostic yield in certain patient populations in whom such genetic alterations play an important role *(8)*. For each patient population, the decision as to which NGS approach and what sequencing depth to use should be based on a careful tradeoff between the per-sample costs, sequencing quality, and consequences for the patient. The results of the present study contribute to making these tradeoffs.

Conclusion

With per-sample costs for WGS of €1669, the acclaimed $1000 genome has not been achieved. To achieve this coveted $1000 genome, not only are long-term and efficient use of the sequencing equipment needed, but also large reductions in capital, and especially consumable costs. Today, WES and TGP are considerably lower-cost alternatives to WGS. Decision makers should be aware of this and carefully weigh the extra costs with the added benefits before implementing WGS as a standard diagnostic test in clinical practice.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: Netherlands Organization for Health. Research and Development (ZonMW) (grant number 40-41200-98-9131).
Expert Testimony: None declared.
Patents: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, and final approval of manuscript.

Acknowledgments: We thank Christian Gilissen and Alexander Hoischen for specifying the technical specifications for data processing and storage and Rolph Pfundt and Erik-Jan Kamsteeg for useful discussion on data analysis and related aspects.

References

1. van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends Genet 2014;30:418–26.
2. Caulfield T, Evans J, McGuire A, Bubela T, Cook-Deegan R, Fishman J, et al. Reflection on the cost of "low-cost" whole genome sequencing: framing the health policy debate. PLoS Biol 2013;11:e1001699.
3. Iglesias A, Anyane-Yebao K, Wynn J, Wilson A, Cho M, Guzman E, et al. The usefulness of whole-exome sequencing in routine clinical practice. Genet Med 2014; 16:922–31.
4. Henderson GE, Wolf SM, Kuczynski KJ, Joffe S, Sharp RR, Parsons DW, et al. The challenge of informed consent and return of results in translations genomics: empirical analysis and recommendations. J Law Med Ethics 2014;42:344–55.
5. Gallego CJ, Bennette CS, Heagerty P, Comstock B, Horike-Pyne M, Hisama F, et al. Comparative effectiveness of next generation genomic sequencing for disease diagnosis: design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes. Contemp Clin Trials 2014;39:1–8.
6. Wetterstrand K. DNA sequencing costs: data from the NGGRI genome sequencing program (GSP). http://www.genome.gov/sequencingcosts/ (Accessed February 2015).
7. Human genome at ten: the sequence explosion. Nature 2010;464:670–1.
8. Xue Y, Ankala A, Wilcox WR, Hegde MR. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single gene, gene panel, or exome/genome sequencing. Genet Med 2014;17:444–51.
9. Illumina. The $1000 genome is here. http://www.illumina.com/systems/hiseq-x-sequencing-system/system.html (Accessed September 2015).
10. Veritas Genetics breaks $1000 whole genome barrier. http://www.prnewswire.com/news-releases/veritas-genetics-breaks-1000-whole-genome-barrier-300150585.html (Accessed September 2015).
11. Service RF. The race for the $1000 genome. Science 2006;311:1544–6.
12. Ng SB, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, et al. Exome sequencing identified the cause of a mendelian disorder. Nat Genet 2010;41:30–5.
13. Vissers LE, de Ligt J, Gilissen C, Janssen I, Steehouwer M, de Vries P, et al. A de novo paradigm for mental retardation. Nat Genet 2010;42:1109–12.
14. Bamshad MJ, Ng SB, Bigham AW, Tabor HK, Emond MJ, Nickerson DA, Shendure J. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet 2011;12:745–55.
15. Bonnefond A, Durand E, Sand O, De Graeve F, Gallina S, Busiah K, et al. Molecular diagnosis of neonatal diabetes mellitus using next-generation sequencing of the whole exome. PLos One 2010;5:e13630.
16. de Ligt J, Willemsen MH, van Bon BW, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med 2012;367:1921–9.
17. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW, Willemsen MH. Genome sequencing identified major causes of severe intellectual disability. Nature 2014;511:344–7.
18. Stark Z, Tan TY, Chong B, Brett GR, Yap P, Walsh M. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. Genet Med 2016.
19. Monroe GR, Frederix GW, Savelberg SM, de Vries TI, Duran KJ, van der Smagt JJ, et al. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. Genet Med 2016.
20. Frank M, Prenzler A, Eils R, Graf von der Schulenburg JM. Genome sequencing: a systematic review of health economic evidence. Health Econ Rev 2013;3:29.
21. Lelieveld SH, Spielmann M, Mundlos S, Veltman JA, Gilissen C. Comparison of exome and genome sequencing technologies for the complete capture of protein-coding regions. Hum Mutat 2015;36:815–22.
22. Sikkema-Raddatz B, Johansson LF, de Boer EN, Almomani R, Boven LG, van den Berg MP, et al. Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum Mutat 2013;34:1035–42.
23. Ghaoui R, Cooper ST, Lek M, Jones K, Corbett A, Reddel SW. Use of whole-exome sequencing for diagnosis of limb-girdle muscular dystrophy: outcomes and lessons learned. JAMA Neurol 2015;72:1424–32.
24. Diekstra A, Bosgoed E, Rikken A, van Lier B, Kamsteeg EJ, Tychon M, et al. Translating Sanger-based routine DNA diagnostic into generic massive parallel ion semiconductor sequencing. Clin Chem 2015;61:154–62.
25. Tan SS, Bouwmans-Frijters CA, Hakkaart-van Roijen L, Handleiding voor kostenonderzoek: methoden en referentieprijzen voor economische evaluaties in de gezondheidszorg. TSG 2012;90:367–72.
26. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. Value in Health 2012;15:835–42.
27. BloombergBusiness EURUSD Spot Exchange Rate. http://www.bloomberg.com/quote/EURUSD:CUR (Accessed December 2015).
28. Amor DJ. Future of whole genome sequencing. J Paediatr Child Health. 2014;51:251–54.
29. Sabatini LM, Mathews C, Ptak D, Doshi S, Tynan K, Hegde MR, et al. Genomic sequencing procedure microcosting analysis and health economic cost-impact analysis: a report of the associated for molecular pathology. J Mol Diag 2016;18:319–28.
30. Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics 2013;14:1833–47.
31. Ajay SS, Parker SC, Abaan HO, Fajardo KV, Margulies EH. Accurate and comprehensive sequencing of personal genomes. Genome Res 2011;21:1498–505.
32. Fang H, Wu Y, Narzisi G, O'Rawe JA, Barrón LT, Rosenbaum J. Reducing INDEL calling errors in whole genome and exome sequencing data. Genome Med 2014;6:89.
33. Shendure J, Akey JM. The origins, determinants, and consequences of human mutations. Science 2015; 349:1478–83.
34. Choi M, Scholl UI, Ji W, Liu T, Tikhonova IR, Zumbo P, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proc Natl Acad Sci U S A 2009;106:19096–101.
35. Amazon. https://aws.amazon.com/ec2/pricing (Accessed September 2015).