Supplementary material 2. Cost modelling protocol

A cost analysis was performed to compare the three genomic testing strategies for AML patients, considering the costs related to each alternative (Figure S3.1). This was accomplished using a Monte Carlo simulation model, which enables incorporating cost data inaccuracy and uncertainty. Only costs that would differentiate among the strategies were included. Furthermore, after consulting with the board member (DM IPO Lisboa), it was decided that 70 percent of the fixed costs of strategy S1 would be included in strategy S2 since IPO Lisboa intends to preserve all equipment and human resources regardless of the chosen strategy.

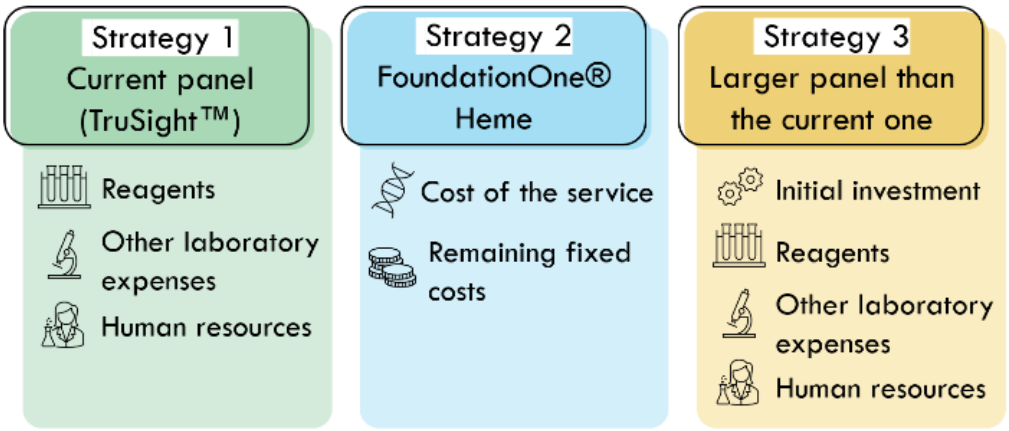

Figure S2.1. Main costs identified for each strategy.

Afterwards, a triangular distribution was assigned to each of these input variables, in order to better describe the associated costs in light of limited availability of data (1). That is, minimum, maximum and expected values were estimated for each input variable of the model (Table S3.1), using 2018 to 2020 accounting reports from UIPM (Unidade de Investigação em Patobiologia Molecular (2)), the unit where the haematology laboratory is included, government sources and consulting with IPO Lisboa experts whenever data was lacking. Data regarding all the equipment purchases made by IPO were consulted to predict the cost of acquiring new equipment, necessary to implement strategy S3. Such purchases might include DNA sequencing machines, bioanalyzer systems and thermal cyclers, and were estimated to be 200 thousand euros. For the minimum and maximum values, a 20 percent deviation was applied to the expected value, which is the approximate variation between different equipment. The

number of human resources involved in the genomic testing process, as well as the annual number of NGS reports, were also estimated.

A period of five years was considered in the cost analysis. On the one hand, many authors suggest the time horizon should be longer in order to capture the major health and economic effects of a genomic technology for the patient and the institution (3). In this case, however, since these are technologies that are evolving at a fast pace and for which there is limited data, and that the health system is still not organized to make later uses of genomic panel data, a shorter 5-years time period was considered. A discount rate of 4 percent was applied when calculating the present value of each group of costs, as suggested by the Portuguese National Authority of Medicines and Health Products (INFARMED) (4).

Table S2.1. Expected, minimum and maximum value of each input variable, used to build the triangular functions for the Monte Carlo simulation model.

Input variable	Most Likely Value	Minimum Value	Maximum Value
Reagents [(1)]	2 621 147 EUR	2 509 985 EUR	2 732 309 EUR
Other expenses [(1)]	89 727 EUR	73 385 EUR	106 070 EUR
Salary [(2)]	172 613 EUR	77 012 EUR	260 247 EUR
FoundationOne [(3)]	5 526 EUR	4 452 EUR	27 643 EUR
Initial Investment	-	-	240 000 EUR
Haematology HR	7	6	8
Annual AML reports	50	40	60
Annual UIPM reports	2300	1800	2800

[(1)] Present cost, considering a period of 5 years; [(2)]Present cost per Superior Technician, considering a period of 5 years; [(3)]Present cost of purchasing one test per year, for a period of 5 years.

Finally, an output function was defined for every strategy, to combine all the existing inputs into the result of the simulation. The output functions for the three strategies are as follows:

$$Cost_1 = \frac{Annual\ AML\ reports}{Annual\ UIPM\ reports} \times (reagents + other\ expenses) + salary \times \text{Haematology } HR \times 0{,}15 \quad (1)$$

$$Cost_2 = FoundationOne \times Annual\ AML\ reports + 0{,}7 \times (salary \times \text{Haematology } HR \times 0{,}15) \quad (2)$$

$$Cost_3 = Inicial\ investment + \frac{Annual\ AML\ reports}{Annual\ UIPM\ reports} \times (reagents + other\ expenses) + salary \times \text{Haematology } HR \times 0{,}15 \quad (3)$$

where $Cost_i$ is the present cost of strategy i considering a time horizon of five years. A factor of 0,15 was applied to the salaries considering that only approximately 15 percent of a hematology technician's time is spent with AML NGS related tasks; and another factor of 0,7 is applied as 30 percent of fixed costs should be inputted elsewhere.

Following the choice of the statistical distributions and the definition of the output functions, the software @RISK, from Palisade (5), was used to perform a Monte Carlo simulation for the three genomic testing strategies. In each iteration, random samples are drawn from the input distributions, from which an output is calculated. After several runs, we obtain an output distribution representing possible cost scenarios and the corresponding probability (6). It was used the @RISK feature in that the number of iterations is automatic, i.e., iterations are performed until all distributions achieve convergence. A statistical analysis can then be performed and used to make decisions regarding the best

course of action. In this case, the number of iterations was set to 'Automatic', meaning that the software performed iterations until all distributions had achieved convergence.

In addition, a sensitivity analysis was performed to understand the effect of each input distribution in the output (see Table S2), which is vital considering the uncertainty surrounding most of the data (3). All results were analysed and validated with the board member (DM IPO Lisboa).

Table S2.2. Output statistics obtained for each genomic testing strategy using a Monte Carlo simulation model.

Output statistics	S1	S2	S3
Mean (EUR)	237.632	754.313	437.922
Minimum (EUR)	131.854	312.645	319.951
Maximum (EUR)	349.527	1.709.732	557.808
Stand. Dev. (EUR)	42.119	278.293	44.140

References

1. Fairchild KW, Misra L, Shi Y. Using Triangular Distribution for Business and Finance Simulations in Excel. Journal of Financial Education. 2016;42(3-4):313-36.
2. IPO Lisboa. Unidade de Investigação em Patobiologia Molecular. [cited 2021 October 10th]; Available from: https://www.ipolisboa.min-saude.pt/centroinvestigacao/unidade-de-investigacao-em-patobiologia-molecular/.
3. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th ed2015.
4. Orientações Metodológicas para Estudos de Avaliação Económica, (2019).
5. Palisade. @Risk. [cited 2021 Sepember 20th]; Available from: https://www.palisade.com/risk/.
6. Raychaudhuri S, editor. Introduction to Monte Carlo simulation. 2008 Winter Simulation Conference; 2008 7-10 Dec. 2008.