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Return on Investment from the Prevention of Orphan Diseases in Kuwait

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ABSTRACT

Spinal Muscular Atrophy type 1 and RPE65 mutation-associated Inherited Retinal dystrophy are two well-known Orphan diseases for having the most expensive Orphan drugs in the market. Being inheritable disorders, they can be prevented through a program that includes Premarital Genetic Screening to detect the defective gene carriers followed by Preimplantation Genetic Diagnosis to identify healthy gametes and In Vitro Fertilization. We developed a stochastic financial model to assess the Return on Investment over five years of implementing a prevention program to tackle these conditions from the financial perspective of the Ministry of Health in Kuwait. The ROI from the prevention program was shown to be highly cost-saving, with a probabilistic average of 9,710,311 USD (2,930,727 KWD). Every 1 USD or KWD spent on prevention would return 1.5 USD or KWD in savings. Meanwhile, not implementing the prevention program could cost the MOH a probabilistic average of 71,431,037 USD (21,555,325 KWD) within the same period. The findings of this study strongly support the adoption and implementation of the prevention program from the financial perspective of the MOH.

Keywords: Spinal Muscular Atrophy, Inherited Retinal Disease, Premarital Screen, Preimplantation Genetic Diagnosis, In Vitro Fertilization.

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Authors' contributions
The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

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Conflict of interest
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1. INTRODUCTION

An orphan disease is a term given for rare disease mostly of genetic origin and of low prevalence defined by the European Commission as affecting less than 1 in every 2000 person [1], while in the United States, it is less than 1 in every 1500 person [2] and Japan, it is less than 1 in every 2500 person [3]. Ironically, Orphan diseases collectively include more than 7000 different conditions [4]. Among these conditions, two genetic conditions stand out for having the most expensive drugs in the market; Firstly, onasemnogene abeparvocec (Zolgensma) costing 2.125 million USD [5], which is indicated for less than two years of age Spinal Muscular Atrophy (SMA) type 1 patients with bi-allelic mutations in the survival motor neuron 1 gene (SMN1) [6] which represent the majority of SMA cases [7]; Secondly, voretigene neparvovec (Luxturna) costing 850,000 USD [8], which is indicated for biallelic RPE65 mutation-associated Inherited Retinal dystrophy (IRD) including Retinitis Pigmentosa and Leber Congenital Amaurosis [9]. In the Arabian Gulf Council countries, these rare diseases have a higher prevalence attributed to the higher rates of consanguineous marriages [10], placing a significant economic and clinical burden on healthcare systems. However, being inheritable disorders, they can be prevented through a program which includes; Premarital Genetic Screening (PMS) to detect the defective gene carriers followed by Preimplantation Genetic Diagnosis (PGD) to identify healthy gametes (male sperm or female egg) and In Vitro Fertilization (IVF) [11].

In Kuwait, a health assessment at the premarital clinic in the Ministry of Health (MOH) for applicants to obtain a marriage license is mandated by legislation. It includes a compulsory set of blood screening tests for six diseases, Human Immunodeficiency Virus, Hepatitis B, Hepatitis C, Syphilis, Thalassemia, and Sickle Cell Anemia [12]. The MOH in Kuwait is a

payer and provider of universal medical care to the citizens, covering all preventive and curative medical care costs, including expensive Orphan drugs such as Zolgensma [13]. As a result, it has a strong incentive to invest in preventing such conditions. This study aims to assess the Return on Investment (ROI) of a prevention program that includes PMS, PGD, and IVF pertaining to SMA type 1 and RPE65-associated IRD from the financial perspective of the MOH in Kuwait over five years.

2. METHODS

We have developed a stochastic financial model in Microsoft Excel (version 16.54) for our ROI approach spanning over a five-year period, in which the investment costs (negative cash flows) include the PMS, PGD and IVF costs while the returns (positive cash flows) include the averted direct medical costs made from prevented cases of SMA and IRD. In addition, the results are reported in terms of Financial Cost Benefit (FCB) where costs are attributed to PMS, PGD and IVF while benefits being the averted costs of prevented cases.

Generally, our clinical, epidemiological and cost data were made stochastic by assigning probabilistic distributions to their average estimates. We have assigned Gamma distribution to the cost data and length of stay since healthcare costs typically have right skewness or heavy right-hand tail [14]. Beta distribution for clinical probabilities and discount rate as they are bounded by (0,1) range [15]. Discrete uniform distribution was assigned for number of applications screened. Furthermore, the costs data in the study were estimated by mixed methods, which involved top-down approach and bottom-up approach for MOH estimates, and reported market value (private sector and international market). Whenever a cost has fixed value without reported standard deviation (SD) we assigned a 5% sensitivity range to that value. Then we run Monte Carlo Simulation with 10,000 iterations to estimate the average estimates of ROI, FCB and total costs or financial burden if there was no prevention program in place.

2.1. Premarital Genetic Screening

We applied an exponential population growth formula on historical numbers of marriage certificates (2016-2020) as registered by Central Statistical Bureau in Kuwait to predict the number of applications in future years (2021-2026), which resulted in a range from 9,666 in the first year to 10,608 applicants in the sixth year. However, to include the worst-case scenario, we assumed that the number of applications would be higher than predicted and range from 10,000 to 12,000. Eventually, we assigned a uniform discrete distribution for the aforementioned range. Detailed estimation is provided in Appendix 1.

As mentioned earlier, current PMS does not include any genetic screening, hence for cost estimation, we investigated the private sector pricing, obtained an average, and assigned stochastic Gamma distribution to it. Detailed estimation is shown in Appendix 2.

2.2. Epidemiology of SMA and IRD

Kuwait Medical Genetic Center (KMGC) in the MOH was established in 1979 and included the national reference laboratory for genetic diagnosis and treatment [16]. Nearly all genetic disorders diagnosed in Kuwait have records in the Center. Expert opinion in the KMGC reported cases of SMA type 1 to be ranging from 3 to 7 cases annually, while the cases of RPE65 mutation-associated IRD to be ranging from 4 to 7 annually for the last decade.

We assumed that the prevention program would prevent less than 50% of these cases annually. Our conservative number regarding averted cases is supported by our knowledge from expert opinion in KMGC of the moderate compliance of parents whose firstborn child was affected by an orphan disease with the PGD and IVF services offered to them, especially if the first attempt of IVF was unsuccessful [17].

2.3. Preimplantation Genetic Diagnosis and In Vitro Fertilization

The MOH, in collaboration with the KMGC, had been advising and offering PGD and IVF services for parents who have one affected child with an orphan or hereditary genetic disease, albeit they reported moderate compliance to the service. The costing of the PGD and IVF were obtained from private sector prices in addition to our MOH estimate. More details are in Appendix 3.

2.4. Costs of SMA and IRD

We estimated the costs of SMA and IRD by the inclusion of the costs of their Orphan drugs and direct medical costs according to clinical guidelines for diagnosis and management of these conditions, which included outpatient visits, emergency departments visit, and hospital admission. Detailed costing for SMA is shown in Appendix 4 and for IRD in Appendix 5.

2.5. Discount rate and currency exchange

Our input for discount rate was 3%, according to recommendations by World Health Organization for healthcare interventions [18]. However, this value was made stochastic by assigning a probabilistic Beta distribution to it, thus covering a wider range of discount values. More detail is in Appendix 6.

All cost estimations are initially done in Kuwaiti Dinars (KWD) currency, later converted to United States Dollars (USD), as shown in Appendix 7.

3. RESULTS

The probabilistic average of ROI of the prevention program over five years is 9,710,311 USD (2,930,727 KWD) with an SD of 5,530,509 USD (1,669,196 KWD) and a 95.71% probability of getting a positive ROI value. The distribution resulting from the Monte Carlo simulation is shown in Figure 1. Meanwhile, the probabilistic FCB is 1.5, with an SD of 0.37. Every 1 USD or KWD spent on prevention would return 1.5 USD or KWD in savings. This result shows that the prevention program is highly cost-saving with a very high probability of getting a favorable outcome. The distribution resulting from the Monte Carlo simulation is shown in Figure 2.

If the prevention program is not implemented, then the probabilistic average of total costs or projected financial burden of these conditions due to direct medical costs over the five years would be 71,431,037 USD (21,555,325 KWD) with an SD of 7,488,163 USD (2,259,659 KWD). The distribution resulting from the Monte Carlo simulation is shown in Figure 3.

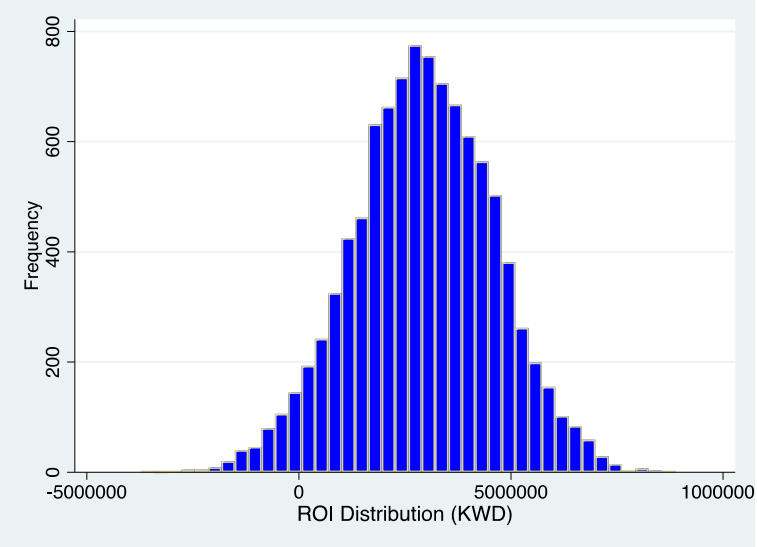

Figure 1: Monte Carlo Simulation Result for Return on Investment Analysis.

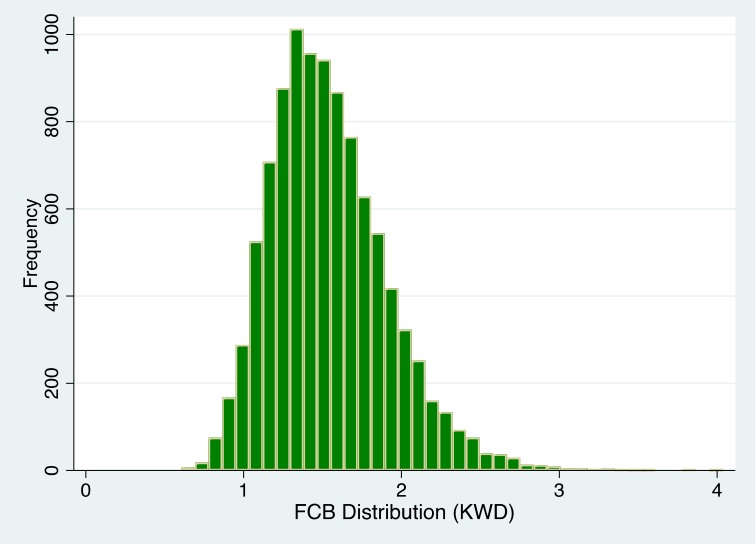

Figure 2: Monte Carlo Simulation Result for Financial Cost Benefit Analysis.

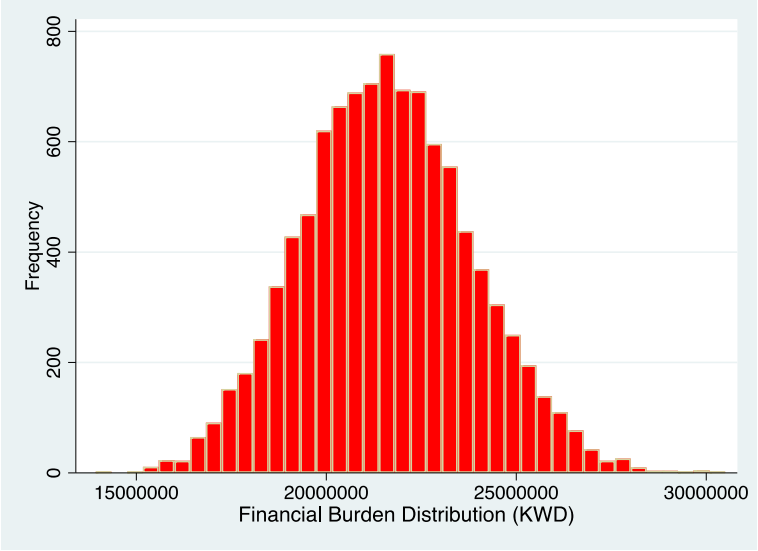

Figure 3: Monte Carlo Simulation Result for Projected Financial Burden.

4. DISCUSSION

The findings of this study provide a strong incentive to policymakers in the MOH and a call for replication elsewhere. We believe that the stochastic nature of the parameters in our model added significant strength and certainty to our estimates. However, our model has a few limitations that need to be addressed.

Firstly, the price for PMS may be overestimated because we obtained private sector prices, which is normally for-profit industry. Nonetheless, the result of the model shows that even with overestimated prevention costs, the prevention program is highly cost-saving. It is worth noting that this might open the door for a public-private partnership, in which PMS can take place in MOH-approved private clinics, which would be reimbursed at competitive fixed rates. Secondly, our estimation of the direct medical costs associated with the diseases may not be comprehensive, albeit the costs of the orphan drugs would dwarf any additional costs. In addition, adding further medical costs will only reinforce our result, making the program more cost-saving.

Thirdly, our model focused on the financial perspective of averting diseases and saving future direct medical costs. In comparison, economic models would encompass personal and societal health benefits such as Quality Adjusted Life Years (QALYs) gained, Disability-Adjusted Life Years (DALYs) averted, social value, and indirect medical costs. The inclusion of the aforementioned health benefits will only reinforce our result. However, it will add significant uncertainty around the valuation and monetization of these health units. On the other hand, we focused solely on real costs and savings to make our financial model more realistic, transparent and straightforward to policymakers and the public. Fourthly, we adopted a conservative approach in assuming worst-case scenarios such as, higher prevention costs and less than 50% prevention rate. A neutral or optimistic scenario would reinforce our result. In contrast, extreme scenarios such as no prevention are theoretically possible, yet we are aware from expert opinion that this is not the case in KMGC.

The final point is that experts recalled the annual number of cases in KMGC. Yet, It is recommended that the KMGC establish a formal national registry for Orphans or rare genetic diseases to monitor epidemiological trends in these important conditions and evaluate the prevention program's effectiveness.

5. CONCLUSION

Over five years, the ROI from the prevention program targeting Spinal Muscular Atrophy type 1 and RPE65 mutation-associated Inherited Retinal dystrophy shown to be highly cost-saving with a probabilistic average of 9,710,311 USD (2,930,727 KWD). Every 1 USD or KWD spent on prevention would return 1.5 USD or KWD in savings. Meanwhile, not implementing the prevention program could cost the MOH a probabilistic average of 71,431,037 USD (21,555,325 KWD) within the same period. The findings of this study strongly support the adoption and implementation of the prevention program from the financial perspective of the MOH.

Appendix 1: Premarital Genetic Screening Applicants Projection

The table below shows the actual number of marriage certificates obtained annually according to the Central Statistical Bureau in Kuwait [19]:

Year	Number of Applications
2016	8800
2017	8735
2018	8824
2019	9246
2020	9481

We applied an exponential population growth formula [20], using the aforementioned historical data to project the number of future applications:

$P = P_0 * e^{RT}$

P: Total population after time "t"
P_0: Starting Population
R: % Rate of Growth
T: Time in Years
e: Euler number (2.71828)

From the aforementioned data, R= 1.9347% and projected population growth is shown in the table below:

Year	Number of Applications
2021	9666
2022	9855
2023	10047
2024	10243
2025	10444
2026	10648

Applications are forecasted to grow from 9,666 in 2021, to 10,648 in 2026.

Appendix 2: Estimating the unit cost of premarital genetic screening tests

We inquired from the private genetic laboratories locally and regionally on the prices to screen a carrier state for specifically 2 conditions, SMA and RPE65 associated IRD as a single panel:

PMS unit cost	Source
95 KWD	Private sector inquiry
110 KWD	Private sector inquiry
120 KWD	Private sector inquiry
150 KWD	Private sector inquiry

We calculated the average to produce the alpha and beta parameters for the stochastic Gamma distribution.

Item	Estimate
Average	118.75 KWD
SD	23.228 KWD
Alpha	26.134
Beta	4.543

Appendix 3: Preimplantation Genetic Diagnosis (PGD) and In Vitro Fertilization (IVF)

Both MOH estimate with private sector locally and regionally were considered in estimating the costs of PGD coupled with IVF:

Item	Cost	Source	Comments
Genetic Counselling	50 KWD	MOH	Mixed methods
IVF procedure	1750 KWD	MOH	Mixed methods
IVF drugs	400 KWD	MOH	Mixed methods
Embryo handling process (biopsy, freezing, transfer cycle)	800 KWD	MOH	Mixed methods
Total	3000 KWD	MOH	

Item	Cost	Source
PGD & IVF	3500 KWD	Private sector inquiry
PGD & IVF	5000 KWD	Private sector inquiry

We calculated the average to produce the alpha and beta parameters for the stochastic Gamma distribution.

Item	Cost
Average	3833.3 KWD
SD	1040.83 KWD
Alpha	13.563
Beta	282.6

Appendix 4: Direct medical costs of Spinal Muscular Atrophy

Orphan drug cost for SMA:

Item	Cost	Source	Comment
onasemnogene abeparvocec (Zolgensma)	640,000 KWD	Market Price [4]	Drug of Choice for SMA in MOH. One dose.
SD	32000 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	1500		Gamma distribution

U.S. Food and Drug Administration drug delivery protocol [6] in Pediatric Intensive Care Unit setting in MOH:

Item	Cost	Source	Comment
Hepatic profile	5 KWD	MOH	Frequency=9
Anti-AAV9 antibody testing	5 KWD	MOH	Frequency=2
Platelet's count	2 KWD	MOH	Frequency=9
Troponin	2.25 KWD	MOH	Frequency=7
Renal profile	4 KWD	MOH	Frequency=4
Complete blood count	2 KWD	MOH	Frequency=1
Corticosteroid	5 KWD	MOH	30 days 1mg/kg assume 8kg = 240mg
Total	99.75 KWD		
SD	4.9875 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	0.2493		Gamma distribution
Outpatient Follow-up	73.16 KWD	MOH	Frequency=8
SD	34.2 KWD	MOH	
Alpha	4.576		Gamma distribution
Beta	15.987		Gamma distribution

Diagnosis and management according to clinical guidelines:

1. Pediatric Emergency Department:

Item	Estimate	Source	Comment
Frequency	5.9	Clinical guidelines [7]	
SD	2.4	Clinical guidelines [7]	
Alpha	6.043		Gamma distribution
Beta	0.9762		Gamma distribution
Unit cost	51.33 KWD	MOH	
SD	44.82 KWD	MOH	
Alpha	1.311		Gamma distribution
Beta	39.135		Gamma distribution

2. Pediatric Intensive Care Unit admission stay, investigations and management:

Item	Estimate	Source	Comment
Average length of stay	29.9	Clinical guidelines [21,22]	
SD	18.1	Clinical guidelines [21,22]	
Alpha	2.728		Gamma distribution
Beta	10.956		Gamma distribution
Unit cost per diem	303.85 KWD	MOH	
SD	150.43 KWD	MOH	
Alpha	4.079		Gamma distribution
Beta	74.474		Gamma distribution

Item	Estimate	Source	Comment
Next generation sequencing neuromuscular panel	100 KWD	MOH	Frequency=1 [23,24]
Video-fluoroscopic swallowing test	57 KWD	MOH	Frequency=1 [23,24]
Total	157 KWD		
SD	7.85 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	0.392		Gamma distribution

Item	Cost	Source	Comment
Complete Blood cells	2 KWD	MOH	Daily [23,24]
Hepatic profile	5 KWD	MOH	Daily [23,24]
Coagulation profile	4 KWD	MOH	Daily [23,24]
Renal profile	4 KWD	MOH	Daily [23,24]
D-dimer	3 KWD	MOH	Daily [23,24]
Arterial blood gases	3 KWD	MOH	Daily [23,24]
Septic screen	10 KWD	MOH	Daily [23,24]
Antibiotics	33 KWD	MOH	Daily [23,24]
Acid suppressants	1 KWD	MOH	Daily [23,24]
Muscle relaxants	2 KWD	MOH	Daily [23,24]
Benzodiazepine	2 KWD	MOH	Daily [23,24]
Supplements	2 KWD	MOH	Daily [23,24]
Total	71 KWD		
SD	3.55 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	0.1775		Gamma distribution

Item	Estimate	Source	Comment
Nasogastric tube probability	0.39	Clinical guideline [7]	Daily [23,24]
Alpha	39		Beta distribution
Beta	61		Beta distribution
Unit cost	25 KWD	MOH	
Alpha	23.66		Gamma distribution
Beta	0.64		Gamma distribution

Item	Estimate	Source	Comment
Gastrostomy tube probability	0.61	Clinical guidelines [7]	Daily [23,24]
Alpha	61		Beta distribution
Beta	39		Beta distribution
Unit cost	640 KWD	MOH	
Alpha	9.287		Gamma distribution
Beta	68.9		Gamma distribution

Item	Estimate	Source	Comment
Mechanical ventilation probability	0.61	Clinical guidelines [7]	Daily [23,24]
Alpha	61		Beta distribution
Beta	39		Beta distribution
Unit cost	190 KWD	MOH	
Alpha	90.25		Gamma distribution
Beta	2.1		Gamma distribution

Item	Estimate	Source	Comment
Non-invasive ventilation probability	0.39	Clinical guidelines [7]	Daily [23,24]
Alpha	39		Beta distribution
Beta	61		Beta distribution
Unit cost	25 KWD	MOH	
Alpha	25		Gamma distribution
Beta	1		Gamma distribution

Item	Cost	Source	Comment
Chest physiotherapy	36.3 KWD	MOH	Daily [23,24]
SD	6.1		
Alpha	35.412		Gamma distribution
Beta	1.025		Gamma distribution

3. Corrective Scoliosis surgery:

Item	Estimate	Source	Comments
Probability	0.04	Clinical guidelines [22]	
Alpha	4		Beta distribution
Beta	96		Beta distribution
Cost	2277 KWD	MOH	
SD	105		
Alpha	470.27		Gamma distribution
Beta	4.841		Gamma distribution

Appendix 5: Direct medical costs of Inherited Retinal Dystrophy

Orphan drug cost for IRD:

Item	Cost	Source	Comment
voretigene neparvovec (Luxturna)	256,000 KWD	Market Price [8]	Drug of Choice for IRD in MOH. For both eyes.
SD	12500 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	1500		Gamma distribution

U.S. Food and Drug Administration drug delivery protocol [9] in Surgical theatre setting in MOH:

Item	cost	Source	Comment
Vitrectomy	685 KWD	MOH	
SD	85 KWD		
Alpha	419.43		Gamma distribution
Beta	610.35		Gamma distribution
Corticosteroid	8 KWD		20 days 1mg/kg assume 20kg = 400 mg
SD	0.4 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	0.02		Gamma distribution

Outpatient follow-up post orphan drug according to clinical guidelines:

Item	Estimate	Source	Comment
Frequency	12	Clinical guidelines [25,26]	4 times in first year and once annually for 8 years
Unit cost	80.25 KWD	MOH	
SD	46.32 KWD		
Alpha	3		Gamma distribution
Beta	26.73		Gamma distribution

Diagnosis and eligibility for Orphan drug treatment:

Item	Estimate	Source	Comment
Frequency	4	Clinical guidelines [26,27]	
Unit cost	80.25 KWD	MOH	
SD	46.32 KWD		
Alpha	3		Gamma distribution
Beta	26.73		Gamma distribution

Item	Cost	Source	Comment
Next generation sequencing ocular panel	120 KWD	MOH	
Full-field electroretinogram	50 KWD	Private sector inquiry	
Fundus autofluorescence	35 KWD	Private sector inquiry	
Optical coherence tomography	40 KWD	Private sector inquiry	
Full field stimulus threshold test	45 KWD	Private sector inquiry	
Microperimetry	40 KDKWD	Private sector inquiry	
Goldmann visual field kinetic perimetry test	35 KWD	Private sector inquiry	
Total	365 KWD		
SD	18.25 KWD	5% sensitivity range	
Alpha	400		Gamma distribution
Beta	0.9125		Gamma distribution

Appendix 6: Discount rate

In the context of global health [28] and with World Health Organization recommendations [18], the typical recommended discount rate is 3%. However, we have assigned this value to a stochastic beta distribution to account for wider range of values.

Item	Estimate	Comment
average	0.03	
SD	0.01	Assumption
Alpha	8.7	Beta distribution
Beta	281.3	Beta distribution

Appendix 7: Currency exchange rate (U.S. Dollar/ Kuwaiti Dinar)

Item	Cost (Kuwaiti Dinar)	Cost (U.S. Dollar)
ROI	2,930,727	9,710,311
SD	1,669,196	5,530,509
FCB	1.5	1.5 (Ratio scale)
SD	0.37	0.37 (Ratio scale)
Total cases (no prevention)	21,555,325	71,431,037
SD	2,259,659	7,488,163

Rate of Exchange: 1 KWD = 3.31 USD [29]
Date of Exchange: October, 28th 2021

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