The Economic Impact of Reverse Personalized Immuno-Oncology

THE CASE OF LATE-STAGE MELANOMA IN ISRAEL

By Curtis W Peterson and Omer Snir

Samueli FOUNDATION

SOCIAL FINANCE ISRAEL

JUNE 2021

The Economic Impact of Reverse Personalized Immuno-Oncology

THE CASE OF LATE-STAGE MELANOMA IN ISRAEL

By Curtis W Peterson and Omer Snir

Samueli FOUNDATION

SOCIAL FINANCE ISRAEL

Table of Contents

Executive Summary

Over 350,000 people are diagnosed with melanoma annually, setting some patients on a short journey of localized treatment and minimal care, while others face a deadly disease that may require years of treatment and a grim prognosis. Even as treatment options for late-stage melanoma (defined as cases where the cancer has moved beyond its original site to other regions in the body) have dramatically improved in the past decade, a significant portion of late-stage melanoma patients will nevertheless succumb to the disease. In addition to the incalculable human cost, economies also suffer when this disease strikes down individuals in the prime of their lives.

In recent years, Professor Gal Markel, supported in part by the Samueli Foundation, has been spearheading work to improve the efficacy of immunotherapy treatment for late-stage melanoma. This research, conducted at the Sheba Medical Center in Israel, has explored the role that fecal microbiota transplantation (FMT) can play in improving treatment by augmenting the immune system of recipient patients. A partnership led by Social Finance Israel, with support from the Israeli HMO, Meuhedet, examined the potential economic impact of FMT on direct and indirect costs of late-stage melanoma treatment as well as long term economic impact.

The results of the analysis were compelling and promising: a conservative estimate projects that offering FMT to eligible late-stage melanoma patients could save the Israeli economy up to ~9 million NIS (net present value) annually. This amounts to roughly 6.5% of the total burden of disease for these patients (137 million NIS). On average, a patient who would survive as a result of adding FMT to their treatment would contribute an additional ~98,000 NIS (net present value) to the economy.

The Samueli Foundation

The Samueli Foundation strives to create societal value by investing in innovative, entrepreneurial and sustainable ideas. The Foundation is guided by the belief that its grants should help to improve the quality of life for all. Through thoughtful investments, the Foundation proactively seeks out agencies that exemplify qualities of creativity, sustainability and entrepreneurial vision. Funding is provided as an investment in the ideas of an agency and its leadership, with the expectation of returns in the form of positive results toward Henry and Susan Samueli's goal of vibrant, healthy and well-balanced communities.

The Samueli Foundation supports the work of Professor Gal Markel's research on reverse personalized immuno-oncology within the Foundation's Integrative Immuno-Oncology Program. Currently, the Samueli Foundation is pursuing the possibility to conduct parallel assessments of the potential impact of reverse personalized immuno-oncology in Israel and in the United States.

Social Finance Israel

Established in 2013, Social Finance Israel (SFI) is a social enterprise that promotes the flow of capital towards solving social issues in Israel, through the use of innovative financing tools. As the first and only social investment intermediary in Israel, SFI developed the impact investing sector with the ultimate goal of positively impacting the lives of citizens nationwide. A cornerstone of SFI's work is the development of social impact bonds (SIBs), of which it is the leading developer in Israel.

Social Finance Israel partners with organizations in Israel and abroad to achieve measurable, positive social outcomes alongside financial returns. SFI also works closely with the Israeli National Advisory Board, which consists of senior executives from the public, financial and social sectors.

Sheba Medical Center

The Sheba Medical Center at Tel Hashomer is a university-affiliated tertiary referral hospital that serves as Israel's national medical center in many fields. Located just outside Tel Aviv, it is the most comprehensive medical center in the Middle East, renowned for its compassionate care and leading-edge medicine. Sheba is also an established research institution that collaborates with biotechnology and pharmaceutical industry partners to develop new drugs, treatments and technologies.

Introduction and Overview

In December 2018, The Samueli Foundation, Professor Gal Markel (a leading researcher on reverse personalized immuno-oncology based at the time at Sheba Medical Center in Ramat Gan, Israel) and Social Finance Israel held a meeting to discuss the preliminary results of Professor Markel's ground-breaking work to treat late-stage melanoma. A Phase I trial, funded in part by the Samueli Foundation, was underway to examine the use of fecal microbiota transplantation (FMT) as a means to improve the efficacy of existing immunotherapy treatments. At this meeting, it was agreed that Social Finance Israel would conduct an economic assessment of the potential impact of FMT as a first step in understanding the real-world impact of reverse personalized immuno-oncology.

The ultimate goal of analyzing the potential implications of the FMT approach is to evaluate the argument that, if successful, it will not only deliver improved health outcomes, but also significant reductions to costs associated with treating cancer as well as other indirect costs. The key question to be answered with an economic assessment is whether the potential economic benefits of FMT are sufficient to warrant both private and public investment to accelerate the development of this approach.

Background

Each year, over 350,000 people are diagnosed with melanoma worldwide. The greatest incidence is noted in Europe and North America, as well as Australia and New Zealand.[1] While treatment for early stage, localized melanoma (melanoma "in situ") carries a minimal cost and high rate of treatment success, melanoma detected at later stages where it has moved beyond its original site (metastasized) often incurs high treatment costs and can lead to death. In the past decade, new treatments based on immunotherapy have replaced or augmented chemotherapy and radiation.[2] This has led to an improvement in survival rates for patients but increased the direct cost of care.[3]

Based on data from the Israeli cancer registry report, 1,151 individuals were diagnosed with late-stage melanoma in 2016 (13.2 men and 10.4 women per 100,000). In the same year, 209 individuals died from late-stage melanoma.[4] Men and Ashkenazi Jews are overrepresented compared to the portion they make of the general population. Historically Israel has been one of the top countries for incidence of melanoma but in recent years, through improved education and early detection, rates of late-stage melanoma diagnosis have declined.[5,6] Nevertheless, the direct and indirect costs of melanoma to the Israeli health care system and economy, not to mention the human cost, are not insignificant.

Health care in Israel is mostly publicly funded via a capitation model that channels money collected through taxes to one of four HMOs *(Kupot Cholim)*. As described in a health system overview report by Rosen et al., all Israeli citizens are guaranteed access to a broad set of basic health services and coverage regardless of age, ethnicity, or employment status.[7] The services each HMO must provide are defined by the law and regulated by the Ministry of Health in the health basket *(Sal Briut)* and, while standardized across HMOs, each HMO has the freedom to determine how to best administer and provide those services. For hospital care, two HMOs operate their own facilities in addition to purchasing services at a negotiated rate, while the rest strictly purchase hospital services. Out-of-pocket expenses for primary care, prescription drugs, and in-patient care are negligible for most patients. This means that in Israel, although socioeconomic status and health literacy contribute to care-seeking behavior and navigation of the system, ability to pay does not limit or restrict treatment for melanoma.[8] Rather, the direct and indirect costs are borne by the government-sponsored system. A summary of the system is visualized in Figure 1.

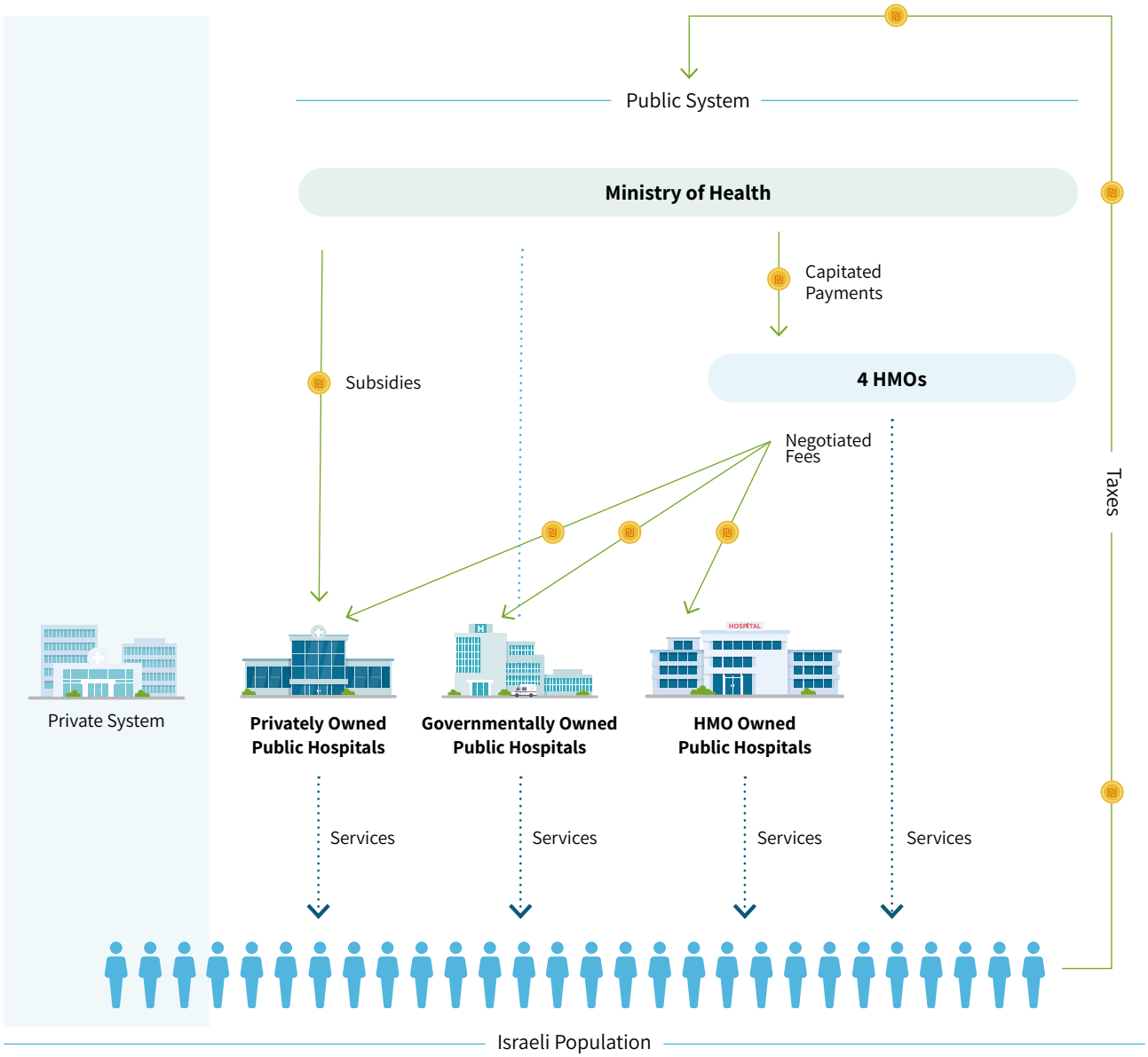

Figure 1. Overview of the Israeli healthcare system.

Treatment Options for Late-Stage Melanoma

Until approximately ten years ago, the standard of care for late stage melanoma was a combination of surgery, chemotherapy and radiation. These treatments showed little success in extending patients' lives, and at the same time significantly diminished quality of life. Overall survival rates for late-stage melanoma with these treatment options lie at less than 5% for five years following the date of diagnosis, with a median survival rate of 8.5 months.[9]

Following the introduction of immunotherapies, prognosis for late-stage melanoma patients changed dramatically.[10] Additional immunologic treatments were developed and approved in subsequent years. These small molecule drugs differ significantly from past treatments and work by activating the body's immune system to target or disrupt specific stages of the biological process required for tumor cell replication. Monoclonal antibodies and checkpoint inhibitors have now replaced chemotherapy and radiation as the standard of care, even as their exact combination and sequencing remains a subject of ongoing research.[11] As a result, overall survival rates for late-stage melanoma have risen to a median of 58 months following diagnosis (just under five years).[12] At the same time, immunotherapies are generally better tolerated by most patients, with significantly fewer side effects and improved quality of life during treatment.[13] Many patients are able to continue their daily lives with minimal disruption compared to those receiving older treatments.

However, while new immunotherapies have enabled many patients to live longer after an initial diagnosis, and in some cases to achieve remission, the experience is not universal. It is not uncommon for a subset of patients to initially respond positively to immunotherapy treatment and experience a period of progression-free survival, only to have their cancer resume aggressive growth.[14] For these patients, immunotherapies can extend life but sadly not prevent them from eventually succumbing to disease. As a result,much of the current research has been focused on understanding why some patients respond better to treatments than others.

A Historic Breakthrough by Professor Gal Markel

Efficacy of a firstline late-stage melanoma immunotherapy treatment (anti-PD-1 therapy) had previously been shown to be influenced by the gut microbiome.[15] Based on this a team led by Professor Markel at Sheba Medical Center initiated a Phase I clinical trial to examine the safety and feasibility of fecal microbiota transplantation (FMT) as a means to positively influence and change the gut microbiome and potentially improve the efficacy of anti-PD-1 treatment in patients with tumors that had previously failed to respond or stopped responding. Ten patients were enrolled in the clinical trial, each receiving transplantation of fecal microbiota from two non-trial melanoma patients who had successfully responded to anti-PD-1 therapy.[16]

The results of the study, published in the prestigious journal *Science*, were positive and received favorable media coverage.[17] Of the ten patients enrolled, three responded: one complete response and two partial responses. Importantly, responses seemed dependent on the FMT donor (no trial participants receiving a transplant from donor two had any clinically significant response), raising the possibility of greater efficacy of FMT based on an improved understanding of donor-dependent factors. Speaking to *The Scientist* on the significance of the trial, Jennifer McQuade of MD Anderson Cancer Center described the results as an "exciting proof of principle to potentially being able to use FMT to augment response to immunotherapy [for] cancer patients."[18]

The Sheba study also determined FMT to be safe and feasible, and demonstrated that it produces microbiome changes in the recipient. These findings in combination with the promising clinical results suggest FMT is a promising therapy that could have widespread adoption and be incorporated into the standard of care for treatment of late-stage melanoma. Similar results from a separate study conducted in the United States were published concurrently, providing additional evidence on the promise of FMT.[19]

Process

To assess the potential economic impact of Professor Markel's FMT treatment innovation, Social Finance Israel led an analysis to create a comprehensive costing model. The goal was to create a model that could suggest the cost-effectiveness of the FMT treatment in combination with existing immunotherapies, and from that analysis to estimate broader effects on the Israeli health care system and economy.

A literature review examined over three hundred peer-reviewed scientific publications and reports, of which approximately fifty were relevant to designing the model and incorporating baseline assumptions on cost and duration of treatment. Several experts in the field were also consulted on costing methodology and pharmaceutical pricing. An initial costing model relied on literature data, which was used to engage an Israeli HMO (Meuhedet) in order to incorporate treatment and costing data specific to Israel.

Meuhedet is Israel's third-largest HMO, serving over a million clients (about 15% of the population) from all sectors across the country. Established in 1974, it operates four district administrative offices and over 300 clinics throughout Israel today.

Meuhedet provided anonymized and aggregated data for patients diagnosed with late-stage (metastatic) melanoma with a date of diagnosis between Jan 2014 and Jan 2017. Based on the approximately one hundred patients identified who met these criteria, a comparison group of similar patients with regards to age and gender but lacking a melanoma or other cancer diagnosis was also generated. Data from the comparison group were used to isolate cancer-related costs from the patients with melanoma group. Anonymized data provided for patients included:

- Age
- Gender
- Melanoma-specific treatments provided, duration of treatments, and cost of treatments
- Additional direct costs (*inter alia* labs, diagnostic radiology, emergency department visits, hospitalization)

The Meuhedet research and ethics committees reviewed and approved all data requests, affirming that patient confidentiality was protected and no patients were put at risk.

Finally, Israel-specific epidemiology, employment, income and retirement data from the Central Bureau of Statistics *(HaLishka HaMerkazit LiStatistika)* and the National Cancer Registry were consulted for inclusion in the model.

Methodology for Costing

To calculate its impact on the Israeli healthcare system and the economy, a cost-effectiveness model was created incorporating direct and indirect costs. This form of analysis compares different treatments or interventions against one another to determine a net gain (or loss) of resources for a specific health outcome (for example, a year of life gained).[20] In this case, the existing standard of care for late-stage melanoma was compared against the standard of care plus FMT. By considering costs (treatment costs and associated medical expenses), and indirect costs (inability to work and reduced productivity due to death or disease), an economic impact can be calculated.

The model was built to take into account the following variables:

- The number of patients in Israel eligible for and receiving treatment for late-stage melanoma
- The cost and duration for various treatment options (including emergency department, hospitalization, lab, radiology, and prescription drug costs)
- Estimated survival rates for various treatments[21]
- Lost wages and contribution to the economy due to death

Data from Meuhedet were used to empirically source direct costs and estimate the percentage of patients across various treatments (including those eligible for FMT).

A summary of data inputs and their sources are summarized in Table 1:

Table 1. Summary of data inputs into costing model

Data Input	***Data Source(s)***
Population and epidemiological data on burden of disease of late-stage melanoma in Israel	Central Bureau of Statistics, Israel National Cancer Registry
Distribution of various late-stage melanoma treatments, average duration of treatment and cost of treatment	Meuhedet
Direct costs associated with late-stage melanoma treatment	Meuhedet
Overall survival rates for patients based on treatment course	Published literature
Employment, income, and retirement age data (to calculate indirect costs)	Central Bureau of Statistics

In order to complete the model, several assumptions were made about various inputs:

- An extrapolation from the FMT Phase I clinical trial results to estimate the impact of FMT on overall survival rate was done assuming a relative 30% increase for the percentage of patients assumed to not survive at each milestone (six months, one year, two years and five years).
- Only first line treatments were considered (consistent with the existing cost-effectiveness literature on melanoma) and only patients treated with monotherapy nivolumab were considered eligible for FMT.
- Direct costs associated with treatment (excluding cost of immunotherapy drugs) were averaged across all treatment groups as a per patient per month cost as data were insufficient to calculate specific to each treatment. This was deemed acceptable as they were not a primary driver of cost.
- Patients who survived five years were assumed to be melanoma-free and have a life expectancy identical to the average population.

Results and Implications

Offering FMT to late-stage melanoma patients receiving nivolumab could save the Israeli economy up to ~9 million NIS (net present value) on an annual basis, which represents ~6.5% of the total burden of disease for these patients (137 million NIS). The majority of these savings come from a decrease in lost contributions to the economy from patients it can be assumed would otherwise succumb to disease. As might be expected, this effect is greater in younger cohorts in which patients have more years of productivity if they survive. On average, a patient who survives contributes an additional ~98,000 NIS (net present value) to the economy over their lifetime. Direct costs for the treatment of these patients (irrespective of receiving FMT) averages 508,000 NIS. Table 2 provides additional details on net economic impact for patients, broken down by age group and gender.

Importantly, the total number of patients considered for this analysis was 92, under ten percent of all Israelis diagnosed with late-stage melanoma annually. Assuming that FMT may positively influence survival rates for patients receiving other treatments (especially combination therapies of nivolumab with ipilimumab), a much larger impact could be anticipated. Beyond Israel, countries with higher rates of late-stage melanoma could benefit considerably as eligible patients represent a larger percentage of the population. These economic benefits are of course in addition to the human element.

Table 2. Summary of treatment cost and lost contribution to economy of patients receiving nivolumab (all numbers are net present value)

Patient population	*Annual # of eligible patients (est.)*	*Treatment cost & lost contribution to the economy*	*Treatment cost & lost contribution to the economy with FMT*	*Net difference due to FMT*	*Net difference per patient*
Men 25-34	2	-₪7,078,247	-₪6,414,021	₪664,226	₪332,113
Men 35-44	5	-₪21,674,838	-₪19,513,161	₪2,161,677	₪432,335
Men 45-54	6	-₪21,562,057	-₪19,485,746	₪2,076,311	₪346,052
Men 55-64	13	-₪24,819,632	-₪22,783,682	₪2,035,950	₪156,612
Men Over 65	24	-₪11,945,885	-₪12,446,002	-₪500,117	-₪20,838
Women 25-34	2	-₪5,270,370	-₪4,817,216	₪453,154	₪226,577
Women 35-44	5	-₪14,440,822	-₪13,150,932	₪1,289,890	₪257,978
Women 45-54	6	-₪12,726,185	-₪11,687,981	₪1,038,204	₪173,034
Women 55-64	10	-₪7,801,024	-₪7,611,617	₪189,407	₪18,941
Women Over 65	19	-₪9,793,473	-₪10,203,479	-₪410,006	-₪21,579
TOTAL	**92**	**-₪137,112,533**	**-₪128,113,837**	**₪8,998,696**	**₪97,812**

Limitations of Analysis

The treatment options made newly available to patients in the past ten years have drastically altered the landscape of melanoma treatments and have benefitted countless patients. Yet the scientific consensus on the most effective duration and sequencing of newer treatments continues to evolve, alongside the growing evidence of their effect on long term survival. This necessitated assumptions around overall survival rates when data were often lacking, simply because these drugs have not been available long enough to measure long term outcomes.

Professor Markel's research on FMT, while promising, was limited to a small number of patients from which population-level effects were estimated. As work on FMT continues, its impact and relevance for use in combination with other treatments in addition to nivolumab will become clearer.

The value of the empirical data provided by Meuhedet cannot be understated; at the same time, Meuhedet members are not fully representative of the Israeli population, and the direct costs provided are likely somewhat less in real life (by approximately 10-30%) as the HMO negotiates payments directly with hospitals and manufacturers.

Suggestions for Further Research

Additional research to calculate the overall costs of late-stage melanoma to the Israeli healthcare system and economy would aid in further contextualizing the potential of FMT. This, in combination with analyses to assess FMT's potential impact in combination with other immunotherapy treatments, would allow for a more complete picture of the impact Professor Markel's work may have. As the promise of FMT is realized and applied to other forms of cancer, the costing model could be adapted to examine similar economic impact.

Acknowledgments

Social Finance Israel and the report's authors wish to thank the following individuals for their support and contribution to this work:

- **Dr. Daniel Goldstein,** Davidoff Cancer Center of Rabin Medical Center
- **Dr. Shmuel Klang,** Meuhedet Research Institute
- **Professor Gal Markel,** Rabin Medical Center and Sheba Medical Center
- **Shahar Merling,** Meuhedet
- **Yaron Neudorfer,** Social Finance Israel
- **Dr. Barbara Silverman**, National Cancer Registry
- **Mike Taylor,** Pharma Evaluation and Bloomsbury Pharma
- **Joan Walter,** The Samueli Foundation
- **Dr. Sofia Wenzler,** Social Finance Israel
- **Dr. Galia Zakay,** Meuhedet

References

1. Karimkhani, C., A.C. Green, T. Nijsten, M.A. Weinstock, R.P. Dellavalle, M. Naghavi, and C. Fitzmaurice. 2017. "The Global Burden of Melanoma: Results from the Global Burden of Disease Study 2015." *British Journal of Dermatology* 177 (1): 134–40. https://doi.org/10.1111/bjd.15510.
2. Rodríguez-Cerdeira, C., M.C. Gregorio, A. López-Barcenas, E. Sánchez-Blanco, B. Sánchez-Blanco, G. Fabbrocini, B. Bardhi, A. Sinani, and R.A. Guzman. 2017. "Advances in Immunotherapy for Melanoma: A Comprehensive Review." *Mediators of Inflammatio*n 2017: 1–14. https://doi.org/10.1155/2017/3264217.
3. Livingstone, A., A. Agarwal, M.R. Stockler, A.M. Menzies, K. Howard, and R.L. Morton. 2020. "Preferences for Immunotherapy in Melanoma: A Systematic Review." *Annals of Surgical Oncology* 27 (2): 571–84. https://doi.org/10.1245/s10434-019-07963-y.
4. The Israeli Ministry of Health. 2019. "Skin Melanoma - updated data on morbidity and mortality" (original title in Hebrew: מלאנומה של העור - עדכון נתוני תחלואה ותמותה). https://www.health.gov.il/PublicationsFiles/Melanoma_11062019.pdf.
5. Reznick, R. "Israel's Skin Cancer Rate Second Highest in the World." *Haaretz*. May 13, 2003. https://www.haaretz.com/1.4718949.
6. Elizera, M. "Skin cancer rates dropping in Israel." *YNet*. June 10, 2017. https://www.ynetnews.com/articles/0,7340,L-4973842,00.html.
7. Rosen, B., R. Waitzberg, and S. Merkur. 2015. "Health Systems in Transition." *Israel Health System Review* 17 (6). https://www.euro.who.int/__data/assets/pdf_file/0009/302967/Israel-HiT.pdf.
8. Ibid.
9. Mansfield, A.S., and S.N. Markovic. 2009. "Novel Therapeutics for the Treatment of Metastatic Melanoma." *Future Oncology* 5 (4): 543–57. https://doi.org/10.2217/fon.09.15.
10. Pasquali, S., A.V. Hadjinicolaou, V.C. Sileni, C.R. Rossi, and S. Mocellin. 2018. "Systemic Treatments for Metastatic Cutaneous Melanoma." *The Cochrane Database of Systematic Reviews* 2018 (2). https://doi.org/10.1002/14651858.CD011123.pub2.
11. Smalley, K.S.M., Z. Eroglu, and V.K. Sondak. 2018. "Combination Therapies for Melanoma: A New Standard of Care?" *American Journal of Clinical Dermatology* 17(2), pp.99–105. https://pubmed.ncbi.nlm.nih.gov/26860106/.
12. Song, Y., A.D. Tieniber, P.A. Gimotty, T.C. Mitchell, R.K. Amaravadi, L.M. Schuchter, D.L. Fraker, and G.C. Karakousis. 2019. "Survival Outcomes of Patients with Clinical Stage III Melanoma in the Era of Novel Systemic Therapies." *Annals of Surgical Oncology* 26 (13): 4621–30. https://doi.org/10.1245/s10434-019-07599-y.
13. Pasquali, S. et al. 2018.
14. Ascierto, P.A., G.V. Long, C. Robert, B. Brady, C. Dutriaux, A.M. Di Giacomo, L. Mortier et al. 2019. "Survival Outcomes in Patients with Previously Untreated BRAF Wild-Type Advanced Melanoma Treated with Nivolumab Therapy." *JAMA Oncology* 5 (2): 187. https://doi.org/10.1001/jamaoncol.2018.4514.
15. Routy, B., E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillère, A. Fluckiger et al. 2018. "Gut Microbiome Influences Efficacy of PD-1-Based Immunotherapy against Epithelial Tumors." *Science* 359 (6371): 91–97. https://doi.org/10.1126/science.aan3706.
16. Baruch, E.N., I. Youngster, G. Ben-Betzalel, R. Ortenberg, A. Lahat, L. Katz, K. Adler et al. 2020. "Fecal Microbiota Transplant Promotes Response in Immunotherapy-Refractory Melanoma Patients." *Science* 371 (6529): 602–9. https://doi.org/10.1126/science.abb5920.
17. Lanese, N. "Cancer Patients Weren't Responding to Therapy. Then They Got a Poop Transplant." *Live Science*. February 4, 2021. https://www.livescience.com/poop-transplants-melanoma-immunotherapy.html.
18. Williams, S. "Fecal Transplant Could Boost Immunotherapy to Treat Melanoma." *The Scientist*. February 12, 2021. https://www.the-scientist.com/news-opinion/fecal-transplant-could-boost-immunotherapy-to-treat-melanoma-68450/amp.

References

19. Davar, D., A.K. Dzutsev, J.A. McCulloch, R.R. Rodrigues, J.M. Chauvin, R.M. Morrison, R.N. Deblasio et al. 2021. "Fecal Microbiota Transplant Overcomes Resistance to Anti–PD-1 Therapy in Melanoma Patients." *Science* 371 (6529): 595–602. https://doi.org/10.1126/science.abf3363.
20. "Cost-Effectiveness Analysis." US Centers for Disease Control and Prevention. 2019. https://www.cdc.gov/policy/polaris/economics/cost-effectiveness.html.
21. Luke, J.J., K.T. Flaherty, A. Ribas, and G.V. Long. 2017. "Targeted Agents and Immunotherapies: Optimizing Outcomes in Melanoma." *Nature Reviews Clinical Oncology* 14 (8): 463–82. https://doi.org/10.1038/nrclinonc.2017.43.