Section 2: English Abstract

Full title of research project

Development of a decision support management tool for optimal utilization of advanced technologies in hospitals

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Key Words

whole genome sequencing; infectious disease; hospital microbiology; analytical hierarchy process; multi-criteria decision-analysis; health policy

Abstract

Scientific Background: The implementation of next generation sequencing (NGS) in hospitals often involves multiple conflicting managerial viewpoints and constraints.
Objectives: To develop a multi-criteria-based decision tool, which considers clinical, operational and economic criteria for optimal integration of microbial NGS in hospitals.
Methodology: The study comprised of four stages: I. A systematic literature review; II. Interviews with experts and stakeholders (n=10); III. Structured survey among specialists and directors of microbiology laboratories (n=52). IV. An analytical hierarchy process (AHP)-based survey among similar population (n=17).
Findings: We identified three main operational models for implementing of NGS: Full In-house full outsourcing and a hybrid model in which the sequencing/analysis components alternate between in-house and outsourcing. Eight main criteria and multiple sub-criteria were identified: cost, manpower, laboratory infrastructure, bioinformatics requirements, computational infrastructure, quality control, motivations, and test goal. Manpower, costs and computational requirements were ranked as most influential on the decision. Multivariable models revealed that participants with vast experience were less likely to rank manpower as an influential criterion (p=0.014) and more likely to rank test goal as influential (p=0.110), for in-house sequencing/analysis. For the majority of criteria and most operational models, there was no difference between the rankings of participants with vast experience and others. The AHP method revealed that the most important criteria were manpower (0.410) for the in-house model, and cost (0.465) for outsourcing model.
Conclusion and Policy Implications: We comprehensively delineated for the first time, different criteria and sub-criteria for the implementation of microbial NGS in hospitals. Our proposed weights represent the relative importance of criteria and sub-criteria and can guide decision-makers with regard to the feasible implementation of NGS in their organization, ahead of effectively implementing NGS in the clinical routine. Further research should validate the results of our study using real-world decisions to implement the technology.

Section 3: Hebrew Abstract

כותרת מלאה של המחקר

פיתוח כלי ניהולי תומך החלטה לשימוש מיטבי בטכנולוגיות מתקדמות בבתי חולים

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מילות מפתח

whole genome sequencing; בתי חולים; מיקרוביולוגיה ;מחלות זיהומיות; analytical hierarchy process; מדיניות בריאות; קבלת החלטות מרובת קריטריונים

תקציר

רקע: ההחלטה להטמיע את טכנולוגית הריצוף מסוג next-generation sequencing (NGS) במתאר האשפוז כרוכה בשיקולים מרובים.
מטרות: לפתח כלי ניהולי תומך החלטה, המבוסס על קריטריונים קליניים, תפעוליים וכלכליים, לצורך שימוש מיטבי בטכנולוגיית NGS באבחון מחלות זיהומיות בבתי חולים.
שיטה: המחקר כלל ארבעה שלבים: I. סקירת ספרות שיטתית; II.ראיונות עם מומחים וקובעי מדיניות (n=10); III. סקר מובנה בקרב מומחים למחלות זיהומיות ומיקרוביולוגיה קלינית ומנהלי מעבדות בארץ ובחו"ל (n=52); IV. פיתוח כלי קבלת החלטות מרובה קריטריונים באמצעות מתודולוגיית analytic network process (AHP) בקרב מומחים אשר השתתפו בסקר (n=17).
ממצאים עיקריים: מופו שלושה מודלים תפעוליים עיקריים ליישום הטכנולוגיה בבתי חולים: 1. ריצוף וביואינפורמטיקה במעבדה המקומית. 2. מיקור חוץ של רכיבים אלה. 3. מודל משולב . בנוסף, זוהו הקריטריונים הבאים: עלות; כוח אדם; תשתיות מעבדה; דרישות ביו אינפורמטיקה; תשתית מחשוב; בקרת איכות; מניע לאימוץ הטכנולוגיה; ומטרת הבדיקה. לפי הראיונות וניתוח תיאורי של ממצאי הסקר, ניכר כי כוח אדם, עלויות ודרישות מחשוב דורגו כקריטריונים המשפיעים ביותר על ההחלטה לאמץ WGS. ברוב הקריטריונים ועל פני רב המודלים התפעוליים, לא היה הבדל בין הדירוג של משתתפים עם ניסיון רב לבין אלו עם ניסיון מועט ב WGS. הדירוג בשיטת AHP העלה שהקריטריון החשוב ביותר בהחלטה להטמעת הטכנולוגיה במעבדה מקומית הוא כח אדם (0.410) ובהחלטה להטמעת הטכנולוגיה במיקור חוץ הוא עלות (0.465).
מסקנות והשלכות מדיניות: מחקר זה מיפה לראשונה באופן מקיף את הקריטריונים ותת הקריטריונים על פני מודלים תפעוליים שונים. אמידת המשקלות המדויקים של הקריטריונים השונים שבוצעה במחקר הנוכחי, מהווה כלי ניהולי בכך שהיא מתארת את החשיבות היחסית של הקריטריונים ותתי הקריטריונים ובכך מסייעת למקבל ההחלטות לזהות את הקריטריונים הקריטיים לאימוץ הטכנולוגיה במודלים התפעוליים השונים בהינתן התנאים והמגבלות הייחודיים למסגרת הארגונית בה מתקבלת ההחלטה. כלי זה צפוי לסייע להטמעה יעילה של הטכנולוגיה כחלק מהשיגרה של תהליך האבחון של מחלות זיהומיות בבתי חולים. מחקר המשך נדרש על-מנת לתקף את ממצאי המחקר הנוכחי באמצעות קבלת החלטות לגבי הטמעת הטכנולוגיה הזו בפועל.

Section 4: Executive Summary- Hebrew

רקע מדעי: טכנולוגית הריצוף מסוג next-generation sequencing (NGS) מובילה למהפכה במיקרוביולוגיה הקלינית. ההחלטה להטמיע אותה במתאר האשפוז כרוכה לרוב בשיקולים מרובים ומורכבים, בהשקפות ובמגבלות שונות. לכן נדרש בירור, הערכה ותעדוף של המודלים התפעוליים, ושל הקריטריונים המעורבים בתהליך קבלת ההחלטה להטמעת NGS.

מטרות המחקר: לפתח כלי ניהולי תומך החלטה, המבוסס על קריטריונים קליניים, תפעוליים וכלכליים, לצורך שימוש מיטבי בטכנולוגיית NGS באבחון מחלות זיהומיות בבתי חולים. בפרט: 1) למפות ולתעדף קריטריונים קליניים, תפעוליים וכלכליים, לצורך שימוש מיטבי בטכנולוגיית NGS בעיקר עבור ריצוף גנומי מלא של חיידקים whole genome sequencing (WGS) – באבחון מחלות זיהומיות בבתי חולים; 2) לבחון האם הקריטריונים הללו ידורגו אחרת במודלים תפעוליים שונים להטמעת הטכנולוגיה; 3) לבחון האם הקריטריונים הללו ידורגו אחרת בקרב מומחים למיקרוביולוגיה בעלי ניסיון רב עם הטכנולוגיה בהשוואה למומחים ללא ניסיון רב.

שיטות המחקר: המחקר כלל ארבעה שלבים: I. סקירת ספרות שיטתית; II.ראיונות עם מומחים וקובעי מדיניות (n=10); III. סקר מובנה בקרב מומחים למחלות זיהומיות ומיקרוביולוגיה קלינית ומנהלי מעבדות בארץ ובחו"ל (n=52); IV. פיתוח כלי קבלת החלטות מרובה קריטריונים באמצעות מתודולוגיית analytic network process (AHP) בקרב תת קבוצה של מומחים אשר השתתפו בסקר שבשלב III (n=17).

בסקירת הספרות אומצה גישה נרטיבית על מנת למפות מודלים תפעוליים, קריטריונים ותת קריטריונים לשילוב WGS - מתוך המקורות שאותרו במאגרי המידע PubMed database ו Web of Science. בשלב II נערכו ראיונות במטרה לאמת ולכייל את הניסוח של המודלים התפעוליים, הקריטריונים והתת קריטריונים שעלו בסקירה השיטתית, ואף להוסיף עליהם, על מנת להבטיח תיאור רחב ומפורט של הבסיס לקבל ההחלטה לשלב באופן מיטבי WGS באבחון מחלות זיהומיות בבתי חולים. בשלב III בוצע מחקר חתך באמצעות סקר נערך במטרה לתעדף את הקריטריונים המשפיעים בעיקר על ההחלטה ליישם WGS על פני מודלים תפעוליים שונים.Kruskal-Wallis test שימש להשוואה בין הדירוג הממוצע של הקריטריונים במודלים התפעוליים השונים. T test (עבור משתנים המתפלגים נורמלית)ו Mann-Whitney U Test (עבור משתנים שאינם מתפלגים נורמלית), שימשו להשוואה בין דירוג הקריטריונים בקרב מומחים בעלי ניסיון רב ביישום WGS לעומת אלו בעלי ניסיון מוגבל. מודל לוגיסטי רב משתני נוסח על מנת לבחון את המשתנים המשפיעים על דירוג הקריטריון כמשפיע ביותר על ההחלטה לאמץ WGS. המשתנה הבלתי תלוי המרכזי בניתוח היה הניסיון של המשיב עם WGS (ניסיון רב הוגדר כריצוף של מעל 111 דגימות בשנה). מודלים אלו תוקננו למשתנים המסבירים הבאים: סוג הארגון (אקדמי לעומת לא אקדמי), ומקום הארגון (EU לעומת השאר). בשלב IV ועל-פי מתודולגיית AHP, נתבקשו המשתתפים לדרג את מידת החשיבות של כל זוג קריטריונים ותתי קריטריונים על-פי המידה שבה אחד יותר חשוב מהשני, בסולם של 1 (חשוב באותה מידה), עד 9 (חשוב הרבה יותר). ערכי

הדירוג הוכנסו למטריצה ומתוכה חושבו המשקל היחסי של החשיבות של כל קריטריון ותת קריטריון. בנוסף, נאמד מדד העקביות וערך ≤0.25 נבחר על מנת לקבוע עקביות.

הממצאים: שלושה מודלים תפעוליים עיקריים ליישום הטכנולוגיה בבתי חולים מופו בשלבים I ו II - של המחקר: 1. ריצוף וביואינפורמטיקה (ניתוח הנתונים) מבוצעים במעבדה המקומית. 2. שירותי ריצוף וביואינפורמטיקה המבוצעים דרך מיקור חוץ. 3. מודל משולב שבו שירותי ריצוף/ביואינפורמטיקה מבוצעים באופן מקומי ושירותי ביואינפורמטיקה/הריצוף מבוצעים על ידי מיקור חוץ. בנוסף, זוהו שמונה קריטריונים עיקריים ותת קריטריונים מרובים המשפיעים על ההחלטה ליישם את WGS - בבתי חולים: עלות (למשל, זמינות המשאבים להשקעה במכשיר הריצוף ובעלות התפעול); כוח אדם (למשל, היכולת לספק תכניות הכשרה או גיוס כוח אדם מיומן); תשתיות מעבדה (למשל, זמינות מכשיר ריצוף וחומרים מתכלים); דרישות ביו אינפורמטיקה (למשל, זמינות של כלי תוכנה אמינים לניתוח הנתונים); תשתית מחשוב (למשל, זמינות שטח אחסון או סידורי אבטחת נתונים); בקרת איכות (למשל, קיומם של נהלים וסטנדרטיים); מניע לאימוץ הטכנולוגיה (למשל, הצורך בבדיקה מהירה יותר, או הצורך בניתוח מידע מקיף ומדויק); ומטרת הבדיקה (למשל, הצורך לבצע חקירת התפרצות או אבחון קליני בזמן אמת או בדיעבד). הסקר העלה כי קריטריונים קליניים, תפעוליים וכלכליים, ולא רק קריטריונים קליניים, אכן נתפסים כמשפיעים על ההחלטה לשלב WGS בתהליך אבחון מחלות זיהומיות בבתי חולים. לפי הראיונות בקרב מומחים בתחום (אך עם ניסיון מוגבל עם WGS) וניתוח תיאורי של ממצאי הסקר, נראה כי כוח אדם, עלויות ודרישות מחשוב דורגו כקריטריונים המשפיעים ביותר על ההחלטה לאמץWGS , בעוד שמטרת הבדיקה והמניע לאימוץ הטכנולוגיה דורגו כמשפיעים פחות. המודלים הרב משתנים מעלים כי ישנו סיכוי נמוך יותר שמשתתף עם ניסיון רב עם WGS (n=26) דרג את דרישות כוח האדם כקריטריון המשפיע ביותר (OR = 0.20, 95% CI: 0.06-0.72, p = 0.014), וכי ישנו סיכוי גבוה יותר בקרב אוכלוסייה זו לדרג את מטרת הבדיקה כקריטריון המשפיע ביותר, אך ממצא זה לא הגיע למובהקות (,OR = 2.61 95% CI: 0.81-8.44, p = 0.110), כל זאת, כאשר גם הריצוף וגם הניתוח נערכים באופן מקומי. לעומת זאת, ברוב הקריטריונים ועל פני רב המודלים התפעוליים, לא היה הבדל בין הדירוג של משתתפים עם ניסיון רב לבין אלו עם ניסיון מועט ב WGS.

הדירוג בשיטת AHP אמד משקלות מדויקים למידת החשיבות של הקריטריון ותת הקריטריון בקבלת ההחלטה להטמיע את הטכנולוגיה. דירוג של 17 מומחים בתחום של מיקרוביולוגיה קלינית נכלל בניתוח. 11 מתוכם עובדים במוסדות אקדמיים, 10 מהם עובדים ב EU ול-13 מהם ניסיון משמעותי בריצוף (קרי, ריצוף של ≤110 דגימות בשנה). חישוב המשקלות היחסיים העלה שכאשר מעוניינים לבצע ריצוף וביואינפורמטיקה במעבדה המקומית (מודל תפעולי 1), אז מידת הזמינות של כח אדם מקצועי היא הקריטריון החשוב ביותר (0.410). הקריטריון הבא בחשיבותו הוא העלות (0.268). תמונת ראי נמצאה כאשר דורגו הקריטריונים עבור המעוניינים לבצע ריצוף וביואינפורמטיקה דרך מיקור חוץ (מודל תפעולי 2, 0.233 לעומת 0.465, בהתאמה). בשני המודלים התפעוליים תשתית המחשוב והביואינפורמטיקה דורגו כקריטריון השלישי בחשיבותו; ותשתיות המעבדה היו הקריטריון הרביעי בחשיבותו. עם זאת, בעוד שכל 4

תתי הקריטריונים תחת תשתיות מחשוב וביואינפורמטיקה קיבלו משקל שווה של חשיבות עבור קבלת ההחלטה כאשר שוקלים ריצוף וניתוח במעבדה מקומית, כאשר נשקל מודל תפעולי של מיקור חוץ, אז קיומן של תשתיות לאבטחת מידע ומשאבי רשת לצורך שיתוף מידע (למשל רוחב פס), הינם בעלי משקל חשוב יותר בהחלטה בהשוואה לתשתית העיבוד והאוטומציה והזמינות של נפח אחסון משמעותי.

מסקנות: למרות היתרונות הפוטנציאליים הרבים של WGS רוב השימוש הנוכחי בגישה זו הוא עדיין מחקרי ולא קליני יישומי. הקושי ביישום הטכנולוגיה בשימוש קליני שגרתי נובע מאתגרים תפעוליים, כלכליים וקליניים. מחקר זה מיפה לראשונה באופן מקיף את הקריטריונים והתת קריטריונים על פני מודלים תפעוליים שונים ליישום WGS באבחון מחלות זיהומיות במסגרות בית חולים, והציג תוצאות של תיעדוף של קריטריונים אלה על פי מקבלי ההחלטות בתחום זה.

השלכות למדיניות והמלצות למקבל ההחלטות: אמידת המשקלות המדויקים של הקריטריונים השונים שבוצעה במחקר הנוכחי, מהווה כלי ניהולי בכך שהיא מתארת את החשיבות היחסית של הקריטריונים ותתי הקריטריונים ובכך מסייעת למקבל ההחלטות להבין מיהם הקריטריונים הקריטיים לאימוץ הטכנולוגיה במודלים התפעוליים השונים בהינתן התנאים והמגבלות הייחודיים למסגרת הארגונית שבהם מתקבלת ההחלטה. בכך, כלי שכזה יכול לסייע להטמעה יעילה של הטכנולוגיה כחלק מהשיגרה של תהליך האבחון של מחלות זיהומיות בבתי חולים. מחקר המשך נדרש על-מנת לתקף את ממצאי המחקר הנוכחי באמצעות קבלת החלטות לגבי הטמעת הטכנולוגיה הזו בפועל.

Section 5: Comprehensive scientific report - English

1. SCIENTIFIC BACKGROUND

Amongst the biggest revolutions of the 20th century are the antibiotics and vaccines, which significantly decreased the prevalence of infectious diseases and their adverse outcomes. Nevertheless, infectious diseases remain in the 21st century a leading cause of morbidity and mortality and are associated with a significant economic burden (e.g. £30 billion a year according to a UK report) [1,2].

Healthcare-associated infections (HAI), are a special threat for public health, and a major contributing factor to medical complications, treatment failure and inpatient mortality and reduced quality of life [2]. Although HAI have been successfully controlled over the years in certain settings, it still remains a major problem, and thus early detection of transmission in the community and hospitals, appropriate antimicrobial treatment and surveillance and control of transmission of new antimicrobial resistant (AMR) strains are of utmost importance [2,3].

In order to control the spread of infection, the clinician should receive expedite information regarding the causative agent and prescribe the right drug (e.g. avoid prescribing antibiotic drugs to viral infections or using too broad a spectrum treatment regimen) in the right timeframe. Diagnostic test performance and turnaround time are central to efficient and judicious care and preventing inappropriate drug prescription, which in turn select for highly resistant pathogens, causes adverse effects and is very costly. Such optimization of infectious disease treatment is a key challenge for healthcare management.

Next generation sequencing (NGS) technology has begun to revolutionize clinical microbiology, but its wide implementation in routine clinical settings is somewhat lagging behind as compared to other disciplines in which its use has become established, such as human genetics, clinical oncology and personalized cancer treatment [4]. Modern clinical microbiology is moving from phenotypic methods, using different assays in order to grow, detect, identify and characterize pathogens in clinical samples based on morphology, and biochemical properties to molecular methods which allow the detection of specific genes that correlate with different phenotypes.

Microbial NGS determines the entire genomic sequence of the microorganism and thus allow characterization of pathogens in an unprecedented fashion, including taxonomical classification, prediction of resistance and virulence and epidemiological subtyping.

Whereas NGS may be applied in a culture-independent manner (i.e. metagenomics), the current study is focused on the application of NGS for whole genome sequencing (WGS) of bacteria downstream to culture isolation [5-7]. WGS has several notable advantages over standard microbiological methods with respect to strain characterization [8-11]. Incorporating WGS for an outbreak investigation may offer a greater degree of resolution underpinning appropriate and timely prevention and control strategies [12-18]. The latter has been shown to be the leading indication for WGS use [9,17]. In depth characterization by WGS may improve turnaround time (TAT) as compared to standard reference microbiology and enhance the technology's affordability [8,13,16,19-27]. In addition, WGS has advantages over traditional methods, for characterization of new pathogens, virulence assessment, and inference of resistance [19,28-32]. However, reported evidence for WGS-based in-silico prediction of AMR had concluded that currently WGS cannot yet replace traditional phenotypic methods [8,19,33].

Taken together, the growing experience with WGS and the increased accessibility and affordability of WGS create great opportunities for improving the management of infectious disease in hospital settings. However, the decision-making process and operational aspects of integrating WGS in routine diagnostic microbiology may be very complex and thus managerial, financial, and clinical criteria must be considered. There is paucity of information regarding criteria and clinical aspects of the integration of WGS in clinical microbiology, especially in routine low-to-medium resource settings, and these knowledge gaps are a significant hindrance for the adoption of this technology in healthcare systems. Thus, the current study is targeted at bridging these knowledge gaps by mapping and prioritizing criteria across different operational models of implementation of WGS for diagnosis of infectious diseases in the hospital setting.

2. RESEARCH OBJECTIVES

The overall aim of this research project is to elicit the fundamental information required in order to enhance the decision-making process for optimal integration of WGS in infectious disease diagnostic processes in hospital setting.

Our specific objectives are:

1) To map and determine the relative importance of managerial criteria supporting the decision to integrate WGS in infectious disease diagnosis in hospitals.

2) To examine whether participants' experience with WGS implementation is associated with the prioritization of criteria of this decision.
3) To examine whether there is difference in the prioritization of criteria across different operational models.

3. RESEARCH HYPOTHESES

Our working hypotheses are that:
1. Clinical, operational and economic criteria (rather than clinical criteria only) will be perceived as influential on the decision to integrate NGS in infectious disease diagnostic processes in hospitals.
2. Infectious diseases and clinical microbiology specialists with vast experience with NGS implementation will prioritize the various criteria differently from those with limited experience.
3. The various criteria will be prioritized differently for different operational models of NGS implementation

4. METHODOLOGY

4.1 Part I: Systematic Review

Search strategy and study selection: We searched the PubMed database and the Web of Science using the following search terms: whole genome sequencing, next generation sequencing, genomic technology, high throughput sequencing, public health, infectious disease, infection control, clinical, pathogen, microbiology, economic, cost, policy, quality control, workflow, operational, infrastructure, resource, prioritization, integration, implementation, incorporation. The reference lists of published articles included in our review relating to operational models or criteria for WGS implementation reviewed in order to capture other relevant studies. The search commenced on October 12th, 2017 and was updated on September 2nd, 2018 with no limitation on publication date. The protocol for this systematic review has been registered on PROSPERO (#CRD42018097360). Two of the authors (JMG and VM) assessed eligibility of the studies independently based on predefined inclusion criteria. Our inclusion criteria were original peer-reviewed articles and reports of recognized professional associations, medical societies and government agencies published in English and discussing the applications of microbial WGS. We excluded non-English articles and reports. In light of

the goals set for the review, we adopted a narrative approach for synthesis of current knowledge.

4.2 Part II: Interviews with experts

In order to devise and articulate the alternative operational models, criteria and sub-criteria that were elicited via the systematic literature review, and to identify additional ones, we conducted face-to-face interviews with ten experts in microbiology, infectious diseases and public health from Israel. Experts and stakeholders were addressed following the recommendation and based on professional acquaintance by one of the advisors (JMG), and participated in the study on a voluntary basis. The interviews took place at the interviewees' workplace and lasted up to 60 minutes. All interviews were recorded and the interviewer (VM) took clarification notes during the interview to minimize omission of information. Data was analyzed simultaneously with its collection in order to continuously articulate and update the list of operational models and criteria. The study protocol was approved by the Human Subjects Research Committee of Ben-Gurion University of the Negev (#1567-1).

4.3 Part III: Online survey

Study population: This cross-sectional survey was conducted among a convenience sample of infectious diseases and clinical microbiology specialists having special interest in advanced diagnostics. Inclusion criteria were: members of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study group for Genomic and Molecular Diagnostics (ESGMD), directors of microbiology laboratories in Israel, and directors of microbiology laboratories abroad (n=250).

Study procedure: The questionnaire was distributed via e-mail (by sending an anonymous link generated by Qualtrics), and participants were recruited on a voluntary basis and were informed that their responses would be kept anonymous. Following respondents' agreement to participate in the study, he/she were asked to complete the questionnaire. In order to increase response rate, reminders were sent twice. The study protocol was approved by the Human Subjects Research Committee of Ben-Gurion University of the Negev (#1693-1).

Study measure: The survey questionnaire was developed by the research group for the purpose of this study. It includes all alternatives operational models, criteria and sub-criteria for integrating WGS in infectious disease diagnostic processes in hospital that were elicited in stages I, II aforementioned. Respondents were asked to prioritize criteria

that mostly influence the decision to implement WGS across different operational models. The questionnaire included two main sections: first, respondents‘ characteristics (personal experience and organizational characteristics), and second, in which respondents were asked to rank the criteria and sub-criteria from the most highly influencing criterion (1) to the least influencing one (6), and across four operational models: full in-house sequencing and analysis; full outsourcing of sequencing and analysis; as well as a hybrid model in which the sequencing/analysis is done in-house and the analysis/sequencing is outsourced.

The *level of experience* with WGS was defined as “limited” if the volume of samples/isolates that were sequenced annually were 100 and below, and as “vast” if the volume of samples/isolates that were sequenced annually were above 100. A dichotomous variable of experience with WGS was defined as “0” for participants with limited experience and “1” for participants with vast experience.

Data analysis: Comparison between the average rankings of criteria in the different operational models was done using Kruskal-Wallis test. Comparison between the rankings of participants with limited and vast experience was conducted by T-test (if the rankings were normally distributed) or Mann-Whitney U Test (if the rankings were not normally distributed). Due to the final distribution of the rankings, the independent variable was defined as “1” if the ranking was 1-4 and zero if otherwise and a logistic multivariable model was specified. The core independent variable was respondent‘s experience (vast vs. limited). Additional predictors in these models included: type of organization (academic vs. non-academic), and location of organization (Europe Union (EU) vs. non-EU). Data were analyzed using STATA software (version 15.1, StataCorp, College Station, TX, USA). P values of ≤0.05 determined statistical significance in all analyses.

4.4 Part IV: Analytical hierarchy process

In this part an analytical hierarchy process (AHP) [34] based survey was conducted among infectious diseases and clinical microbiology specialists having special interest in advanced diagnostics, including directors of microbiology laboratories in Israel and abroad (n=40). AHP is not a statistically based methodology and it is acceptable to use a small sample size to achieve technically valid results [34-36]. Participants were asked to provide their answers to pairwise questions, such as: “for incorporating NGS in infectious disease diagnostic process, how much more important is criterion *i* to criterion *j*? on a 9-

point scale, where 9 indicates extreme importance and 1 indicates equal importance of one criterion over another. A pairwise comparison was performed for all criteria and sub criteria (that were mapped in the previous parts of the study), and for two non-hybrid operational models: full in-house and full outsourcing. Respondents' answers were entered to a pairwise comparison matrix and the eigenvectors were then computed. In order to confirm that participants' preferences ratings were consistent, we computed the consistency ratio. An acceptable value of the consistency ratio value was ≤0.25. The AHP model was solved using the Microsoft Excel (2016).

5. FINDINGS

5.1 Part I: Systematic Review

The Systematic Review was recently published in a Q1 journal [37]. Our original search identified 1,558 articles (first search and updating search excluding duplicates). Of those, 1,408 were excluded based on their title and/or abstract by both reviewers, 2 full-text version were not available and 1 was not in English. The remaining 147 papers were assessed based on their full-text. Six additional articles were identified through reviewing of the reference lists of the 147. Fifty-five of them were excluded mainly since they were not relating to the implementation of WGS for diagnosis of infectious diseases and/or did not address microbial genomics or managerial aspects of implementation of the technology. Hence, 98 articles were included in the systematic review (see Figure 1, p.1088 in [37]).

Alternative operational models for integration of WGS: Sixteen articles that were included in our review discussed operational models for implementing WGS. Principally, four main alternative operational models for incorporating WGS in clinical microbiology laboratories emerged from the review of the literature: 1. Full In-house sequencing and analysis services 2. Full outsourcing of sequencing and analysis services. 3. Hybrid model in which the sequencing is done in-house and the analysis is outsourced. 4. Hybrid model in which the analysis is conducted in-house and the sequencing is outsourced. An additional operational model, involves sequencing and analysis services are offered by public laboratories at a national level and are free of charge, as part of mandatory surveillance. Such a centralized operational model is out of the scope of the current review since it does not necessitate development of decision-making criteria.

It was argued that in-house sequencing and analysis would be more responsive to clients' needs due to the end-to-end availability of experts and the entire required infrastructure and the faster TAT [38]. To achieve a clinically relevant TAT, the in-house model will involve analysis of samples, in small batches or even individual urgent samples. This in contrary to other goals such as molecular epidemiology (in non-outbreak situations), where the analysis typically involves larger batches [39,40]. Adoption of an in-house model would facilitate a smooth transitioning from traditional methods compared to large national or international networks, where all laboratories must implement the same methods and standards, a process that may be hampered by disparities in trained staff and budget constraints [24]. That said participation in WGS networks may also facilitate the leap into genomics, especially in settings with lower resources.

Outsourcing of both sequencing and analysis services may be preferable for small- to mid-size hospitals, especially those who cannot afford capital investments required for creating the sequencing and bioinformatics infrastructure. Larger hospitals that process a higher sample throughput, might prefer an in-house model. However, at peak demands, such as in disease outbreak, even large hospitals may need to rely on the outsourcing model [41,42]. Using the outsourcing model for sequencing may pool isolates from smaller laboratories to fill the required standardized sequencing run, and that may improve overall flexibility, quality, time and cost efficiency of sequencing [4,17,43-45]. Outsourcing of analysis services by online computational cloud might stimulate research collaborations and faster response to outbreak scenarios [41]. However, additional challenges may include assuring adherence to ethical standards (e.g. data safety and privacy) as well as regulatory considerations.

The **hybrid model** incorporates in-house services with complementary outsourced services and enhances the need for high TAT with advanced resources and expertise [38]. Outsourcing can be applied for the sequencing and/or bioinformatics while some preparatory step and post-analytical steps are almost always performed in-house [16]. This model may result in slower TAT compared to in-house model [16,46], yet may minimize computational and technical support costs [46].

A survey from research settings (rather than acute-care hospital) revealed that 58% (19/33) and 45% (15/33) of researchers reported that they used NGS platforms in a core facility at their institution or in a collaborating academic lab, respectively. The minority this group used their own sequencer at their laboratory (13% (4/33)). In addition, the majority

of NGS users reported that they were analyzing sequencing data within their own laboratory although choices for using in-house or outsourcing services are made upon the needs of each individual project [47]. On the other hand, the European Centre for Disease Prevention and Control (ECDC) survey in 2016, among national laboratories, revealed that the access to bioinformatics expertise for routine data analysis in EU countries was limited [48]. Another survey in which most respondents were clinical microbiologists or infectious disease physicians revealed that WGS-based diagnosis would most likely be used in reference laboratories or in very large hospitals due to lack of in-house bioinformatics expertise and because of cost concerns [17]. On the other hand, a survey of end-users' requirements and attitudes towards an NGS proficiency testing, mainly among researchers and public health professionals highlighted that most respondents had internal NGS capabilities (84%(38/45)) [9].

Criteria for integration of WGS: Six main criteria and multiple sub-criteria that influence the decision to implement WGS in hospitals emerged from the systematic literature review: 1) cost (e.g. the availability of resources for capital and operational investment); 2) manpower (e.g. the ability to provide training programs or recruit trained personnel); 3) laboratory infrastructure (e.g. the availability of supplies and consumables or sequencing platforms); 4) bioinformatics requirements (e.g. the availability of valid analysis tools); 5) computational infrastructure (e.g. the availability of storage space or data safety arrangements); 6) quality control (e.g. the existence of standardized procedures). Detailed description of these criteria and sub-criteria was recently published by our group [37].

5.2 Part II: Results of the interviews

Four of the interviewees were directors of public health laboratories (DPHs), three were directors of hospital-based clinical microbiology laboratories (DCMs), and 3 were heads of infectious disease units within hospitals (HIDs). Five of the interviewees had some knowledge regarding NGS technology but without actual experience, however some of them had comprehensive knowledge compared to others. Two of these five interviewees were DPHs, that take part in decision making of health policy in Israel, and three of them were DCMs. The other five interviewees included two DPHs and three HIDs who have already adopted NGS to some extent, in a restricted manner, according to specific research question and not as part of a routine use. We focused mainly on three aspects during the interviews: 1. The most plausible/preferable operational models for

incorporating WGS in infectious disease diagnostics; 2. The criteria for implementing WGS in clinical practice; and 3. Insights with regard to a useful managerial decision tool for WGS implementation in the hospital settings.

Aspect 1: Interviewees were asked to delineate alternative operational models for incorporating WGS in clinical microbiology, which includes the pre-sequencing step (DNA extraction), sequencing and bioinformatics analysis. They mentioned all models that emerged from the systematic literature review. Participants were asked about the most plausible/preferable operational model to incorporate WGS. Three interviewees, all DPHs, argued that the first priority is that both sequencing and analysis will be conducted in-house. However, five interviewees (3 DCMs, 1 HID and 1 DPH) preferred full outsourcing as the first priority for implementing WGS. Only one, a HID, chose the hybrid model as the first priority.

Participants differentiated between the need to procure a sequencing device and the need to hire bioinformatics experts as well as the availability of bioinformatics platforms for in-silico analysis. Five out of nine interviewees (one of the interviewees did not address this issue), 3 DCMs, a HID and a DPH, argued that it is preferred to use the sequencer at a core institutional facility, that may be used for various applications, such as human genomics in cancer and genetics. While two of them, both DPHs, had stressed that, ideally, it should be purchased by the local laboratory, however, due to cost constraints it would not be materialized at the beginning. Two out of the nine interviewees, a HID and a DPH, emphasized that it is only possible that an institutional core facility will purchase the sequencing device. They all agreed that choosing the right device depends upon WGS application (i.e. test goal). A DPH argued that in the publicly financed health system in Israel, the decision to purchase a device or services should be based on a tendering process that complies with applicable law. The provider needs to be recognized and validated by the Ministry of Health, and this required approval is another bureaucratic challenge for implementation.

With regard to the need to hire bioinformatics experts, five out of seven participants, that addressed this issue (three DPHs, a DCM and HID) emphasized that the analysis should be implemented in-house. A DPH said, that before completion of bioinformatics training of the laboratory staff, it is inevitable to outsource the analysis services. However, following completion of the training program, bioinformatics should be conducted in-house. Other interviewees reported that the analysis should be outsourced through an expert center

harboring all the facilities of platforms and staff, addressing all stages of the infectious disease diagnosis process (from DNA extraction and sequencing to analysis and reporting).

The majority of the interviewees indicated that the preferable operation model for implementation depends upon the test goal. A DPH highlighted that the purpose for using WGS should be clearly defined. Two DCMs, a HID and a DPH highlighted that an important criterion that will facilitate adoption of WGS in clinical practice is the criticality level of faster TAT. When the goal is molecular epidemiology (i.e. a non-real time outbreak investigation), three interviewees thought that sequencing device should not be purchased by the hospital and the bioinformatics should be outsourced, since there is no need for real-time results. In the contrary, when the goal is clinical diagnosis or real time outbreak investigation, WGS should be conducted in-house, in order to be amenable to faster TAT, for both sequencing and analysis. Two experts added that when the goal is investigating outbreaks, analysis should be implemented in-house, due to the need for tailored and precise answers for the investigated questions. However, another two interviewees emphasized that analysis and sequencing, for cases of clinical diagnosis or outbreak investigation, might better be outsourced through one central unit, providing different platforms for various applications of specific investigated questions, for real-time demands and will provide quality and fast results. Two interviewees emphasized that for all test goals, sequencing and analysis should be outsourced through one central unit.

Aspect 2: Participants were asked to detail the clinical, operational and economic criteria that need to be considered when implementing WGS in infectious disease process in hospitals and to prioritize them by importance.

Manpower requirements were ranked by 8 interviewees (three DPHs, three HIDs, and two DCMs), as the most crucial and significant criteria that influence the decision to implement WGS. The ability to manage and analyze big data depends on high proficiency in data interpretation which requires training programs and personal skills. Some interviewees emphasized that part of the training programs should be addressed by universities, and should be adjusted particularly to the clinical field. Two DPHs argued that it is important to consider the feasibility and potential effectiveness of applying training programs in bioinformatics of existent laboratory personnel. Two interviewees, one HID and one DPH, said that establishing posts for bioinformaticians within clinical laboratory is mandatory.

Cost: Five of the interviewees (two DCMs, two DPHs and one HID), reported that they have already used this technology, but except for one that uses it more often, the others seldom use it and mostly for research. Still, most of the interviewees reported that they do not have comprehensive information regarding market costs in a way that enables making rational decisions. Even though it was agreeable that NGS technology could not be implemented without a designated budget, the expenditures on devices and complementary computation and software, was ranked by 8 interviewees (two HIDs, three DPHs, three DCMs) as the second most important criterion that influences the decision to implement WGS. Only one, a DCM, ranked cost as the first most important criterion. In spite of the significant challenge of cost, five participants (two HIDs, two DPHs and one DCM) emphasized that it is often easier to allocate budget for non-recurring expenses (such as for sequencing device) rather than for recurring costs (for example monthly wages). It is even easier if the sequencing platform is purchased for an institutional core facility, and thus provides services for multiple users and various test goals. One participant, a DPH, mentioned in this regard that the monthly salary for a bioinformatician is twofold compared to other lab worker. One interviewee which is a DCM, said that the cost of purchasing a sequencing device varies according to its technological features, some are more powerful and capable of multi-processing than others, while others provide manipulation on genome in high complexity, and thus eventually they suit different applications. Two interviewees (a DPH and a HID) said that outsourcing of sequencing is cheaper per test than handling its fixed costs and those costs of sequencing could be decreased by mutual collaborations between users and sequencing services suppliers. Additionally, library preparation which includes laboratory supplies, kits and consumables cost (i.e. for the pre-sequencing step) was mentioned, by one DPH, as the most significant sequencing costs. However, another DPH said that multi-processing could make it cheaper by handling a batch of samples in parallel. Four participants, two DCMs, a HID and a DPH, added the importance of having evidence of cost-effectiveness of implementing WGS in the clinical field over currently used methods, before deciding to implement WGS. A HID and a HCM argued that managers are encouraged to adopt advanced technology despite the considerable investment involved, since it has the potential to contribute to the institutional prestige.

Quality control of WGS applications was mentioned by 8 participants as a criterion to be considered before implementing WGS. This criterion was mentioned as the first and

second most important criteria by DPH and by a HID, respectively. Interviewees stated that accreditation process of sequencing and analysis requires quality control and validation of the process using standard and acceptable protocols, especially for the step of pre-sequencing (e.g. DNA extraction and library preparations), which is fundamentally important for achieving precise results and reproducibility. Another DCM said that if the goal of using WGS is outbreak investigations, then the accreditation process would be easier due to the fact that there is already some consensus regarding using WGS for investigating outbreaks.

Computational infrastructure: Three participants, a DCM and two DPHs, ranked this criterion as less influential (as the third, fourth and sixth most preferable criterion). They referred to data security and privacy requirements as an important criterion for the implementation decision, especially when it is metagenomic data and when it is stored in the cloud.

Aspect 3: The last issue that the experts were asked to address was the characteristics of a future managerial decision-making tool that might help them to decide if, when and how to implement WGS technology. Four participants, a HID, two DPHs and a DCM, thought that a ―checklist‖ of all criteria and sub-criteria for this decision would be helpful for prioritizing the best operational model for implementing WGS. One of the interviewees added that this decision might not be perceived as significant compared to other decisions that the managers face annually. Thus, this "checklist" should contain specific criteria that will be adjusted to the specific context, namely the organization‘s characteristics, the decision makers' point of views with regard to ethics and equity. One DPH was in favor of the idea of developing a managerial tool, however, not for the initial decision concerning implementation of WGS, but rather for prioritizing the clinical scenarios by the extent to which WGS would be beneficial over currently available methods. Another DPH said that a decision tree might be useful if it will present the pros and cons of implementing WGS for each criterion against currently used technologies (two sides of the coin).

As part of the interview, the experts were asked whether governmental incentives or regulations could promote the implementation of new technologies and whether they are familiar with such incentives or regulations. Only two participants, both DPHs, addressed this question. One said that incentives for adopting WGS for outbreaks could be beneficial due to the already proven effectiveness of WGS in outbreaks investigation. The

other said that policy or regulations could be applied according to the extent that the test is necessary. That person said that if the test was significantly beneficial and can contribute to a large population (significantly improve public health), then the regulator should enhance its implementation. The DPH added that governmental incentives could be defined with relation to quality indices of infection prevention in hospitals (similar to incentives applied in other clinical field, such as neonatal intensive care units or influenza vaccination), and this might promote WGS adoption while improving health outcomes.

5.3 Part III: Online survey

Characteristics of study population

Seventy-seven participants started answering the online questionnaire. Twenty-five of them did not complete the core part of the questionnaire (ranking the criteria) and thus were not included in the analysis. The remaining 52 respondents were eligible for analysis. The organizations to which 34 respondents belonged (65%) were located in the European Union (EU), while 18 (35%) were located in other countries (other European countries (n=7, 13%), Saudi Arabia (n=1, 2%), South Korea (n=1, 2%), Hong Kong (n=1, 2%), Qatar, Pakistan (n=1, 2%) and Israel (n=5, 10%)). Twenty-eight respondents (54%) worked in non-academic organizations (Governmental (n=12, 23%), other public institution (n=11, 20%), private ownership/industry (n=4, 8%), university hospital (n=1, 2%)), and 24 worked in academic institutions (46%). The distribution of respondents' professions was as following: clinical microbiologists (n=26, 50%), laboratory scientists (n=15, 29%), infectious diseases specialists (n=3, 6%), genomic scientist (n=1, 2%), bioinformaticians (n=3, 6%), manager (n=1, 2%), medical molecular microbiologist (n=2, 4%) other (n=1, 2%).

Research hypothesis 1: Table 1 presents the ranking of the main criteria. It demonstrates that manpower requirements, costs and computational requirements were ranked as the most influential on the decision to integrate WGS in infectious disease diagnostic processes in hospitals, while the test-goal was perceived as less influential. Thus, our results support hypothesis 1, namely, operational and financial criteria rather than solely the clinical criteria are the drivers for the decision to implement NGS in the hospital setting.

Research hypothesis 2: The univariable analysis between the rankings of participants with limited and vast experience across the different operational models revealed that there was significant (or marginally significant) difference in the rankings of

manpower requirements (p=0.018) and test-goal (p=0.069) in a model in which both sequencing and analysis are conducted in-house, and in the ranking of test goal (p=0.119) in a model in which sequencing is conducted in-house and analysis is outsourced. Thus, the multivariable analysis was conducted only for those three variables.

The multivariable logit model for determinants of manpower requirements as the most influential criteria when both sequencing and analysis are conducted in-house revealed that participant with vast experience with WGS were less likely to rank manpower requirements as an influential criterion (OR=0.20, 95% CI: 0.06-0.72, p=0.014). The multivariable logit model for determinants of test goal as the most influential criteria when both sequencing and analysis are conducted in-house showed that participants with vast experience with WGS were more likely to rank test goal criterion as influential with borderline significance (OR=2.61, 95% CI: 0.81-8.44, p=0.110). The multivariable logit model for determinants of test goal as the most influential criteria when sequencing is conducted in-house and the analysis is outsourced demonstrated that experience with WGS was not associated with the ranking of this criterion (OR=0.45, 95% CI: 0.14-1.47, p=0.184). Thus, our results partially support hypothesis 2.

Table 1. Ranking of the six criteria across different operational models

Criteria	Both sequencing and analysis are conducted in-house	Both sequencing and analysis are outsourced	Analysis is conducted in-house and the sequencing is outsourced	Sequencing is conducted in-house and the analysis is outsourced	p-value
Manpower	3.12 ± 2.02 (2)	2.52 ± 1.41 (2)	2.54 ± 1.65 (2)	2.43 ± 1.37 (2)	0.584
Cost	3.17 ± 1.87 (3)	3.21 ± 1.79 (3)	2.92 ± 1.66 (2)	2.75 ± 1.60 (2)	0.596
Bioinformatics	2.92 ± 1.51 (3)	3.10 ± 1.49 (3)	3.06 ± 1.46 (3)	3.06 ± 1.83 (2)	0.897
Laboratory infrastructure	3.35 ± 1.43 (3)	3.37 ± 1.60 (4)	3.31 ± 1.54 (3)	3.55 ± 1.27 (4)	0.762
Motivation	3.77 ± 1.49 (4)	4.21 ± 1.49 (5)	4.27 ± 1.48 (5)	4.27 ± 1.50 (5)	0.175
Test goal	4.58 ± 1.38 (5)	4.60 ± 1.65 (5)	4.90 ± 1.24 (5)	4.94 ± 1.24 (5)	0.514

Values are mean ± SD (median)

The multivariable logit model for determinants of manpower requirements as the most influential criteria when both sequencing and analysis are conducted in-house revealed

that participant with vast experience with WGS were less likely to rank manpower requirements as an influential criterion (OR=0.20, 95% CI: 0.06-0.72, p=0.014). The multivariable logit model for determinants of test goal as the most influential criteria when both sequencing and analysis are conducted in-house showed that participants with vast experience with WGS were more likely to rank test goal criterion as influential with borderline significance (OR=2.61, 95% CI: 0.81-8.44, p=0.110). The multivariable logit model for determinants of test goal as the most influential criteria when sequencing is conducted in-house and the analysis is outsourced demonstrated that experience with WGS was not associated with the ranking of this criterion (OR=0.45, 95% CI: 0.14-1.47, p=0.184). Thus, our results partially support hypothesis 2.

Research hypothesis 3: The comparison between the rankings of the six criteria across the four operational models is depicted in Table 1. Our results demonstrate that there was no significant difference in the ranking of manpower (p=0.584), cost (p=0.596), computational and bioinformatics (p=0.897), laboratory infrastructure (p=0.762), motivations (p=0.175) and test goal (p=0.514), across the different operational models. Thus, our results did not support hypothesis 3.

5.3 Part III: Analytical hierarchy process

Twenty-one participants began answering the online AHP questionnaire. Four of them did not complete the core part of the questionnaire (ranking the criteria) and thus were not included in the analysis. The remaining 17 respondents were eligible for analysis. Twelve participants were clinical microbiologists, 3 were laboratory scientists, and 2 were bioinformaticians. Most of participants (n=11) worked in academic institution, located in the European Union (n=10), and reported sequencing >100 samples/isolates annually (n=13). The participants perceived weights of each criteria and sub-criteria are presented in Table 2.

The AHP method revealed that if one considers conducting both sequencing and downstream analysis locally, the most important criteria for incorporating WGS in the infectious disease diagnostic process in hospital is manpower (0.410). The second most important criteria in this case is costs (0.268). The opposite ranking was observed when considering to outsource both sequencing and downstream analysis (0.233 and 0.465, respectively). In both operational models computational and bioinformatics requirements was ranked as the third most important one; and laboratory requirements were ranked the

fourth, for both operational models (Table 2). While all four sub-criteria of computational and bioinformatics requirements had similar weights if both sequencing and analysis are conducted locally, if an outsourcing model is considered, then the existence of appropriate arrangements and infrastructure for data safety and security and networking capabilities (adequate band width, data sharing) are relatively more important than the scalability hardware and software (processing power, automation), and the availability of adequate storage space capacity.

Table 2. The importance weight of the criteria and sub-criteria by the operational model

Criteria	Sub-criteria	Full in-house	Full outsourcing
Manpower requirements		**0.410**	**0.233**
	The ability to provide **training program** for existing laboratory personnel	0.196	0.143
	The ability to **recruit trained personnel**	0.214	0.090
Costs		**0.268**	**0.465**
	Available **resources for capital investment** (laboratory equipment, data storage space, software costs)	0.150	0.236
	Available **resources for variable costs** (e.g. laboratory supplies and consumables and salaries)	0.118	0.229
Computational and bioinformatics requirements		**0.204**	**0.175**
	The scalability **hardware and software** (processing power, automation)	0.055	0.031
	The existence of appropriate arrangements and infrastructure for **data safety and security**	0.053	0.049
	The existence of **networking capabilities** (adequate band width, data sharing)	0.045	0.060
	The availability of adequate **storage space capacity**	0.051	0.036
Laboratory requirements		**0.118**	**0.127**

6. DISCUSSION & CONCLUSIONS

Microbial genomics have been gaining momentum in recent years and evidence is accumulating around the world concerning the various advantages of this method. WGS has been praised especially in its role in the investigation of outbreaks [9,12-18,49,50], detection of resistance mechanisms and tailoring antibiotic treatment, vaccine development [51], improvement of patient outcomes and reduced treatment cost [52], and

diagnostic performance over conventional tests [53,54]. In spite of the potential benefits of this approach, most of its current use is still research rather than in routine clinical care. The difficulty in the implementation of the technology in routine clinical use stems from multiple operational, financial and clinical challenges. The current research sought to map these challenges systematically and prioritize them across different operational models for implementing WGS in hospital diagnostics through interviews and survey among experts in this field.

According to the systematic review and interviews, there are four main possible operational models for implementing the technology within hospitals, depending on in-house vs. outsourced performance of the ‘wet‘ and ‘dry‘ lab components. Our systematic review and interview identified six main criteria and multiple sub-criteria that influence the decision to implement WGS in hospitals: cost, manpower, laboratory infrastructure, bioinformatics requirements, computational infrastructure, and quality control. Our face-to-face interviews added two criteria regarding the decision to implement WGS: motivation (e.g. the need for faster turnaround time, the need for comprehensive analysis, the availability of evidence that the technology is cost-effective, the need to respond to client demand and the need to improve institutional reputation); and test goal (e.g. the need to conduct real-time or retrospective outbreak investigation; the need to conduct real-time or retrospective clinical diagnostics or the need to conduct research). Our survey and interviews revealed that that manpower, costs and computational requirements were ranked as most influential on the decision to integrate WGS, while test goal and motivation were ranked as less influential. In addition, our multivariable models revealed that for the majority of criteria there was no difference between the rankings of participants with vast experience and those with limited experience with WGS. The AHP method suggests that the importance weight of the various criteria and sub-criteria are dependent on the operational model considered. Specifically, if one considers in-house sequencing and downstream analysis, the most important criteria for incorporating WGS in the infectious disease diagnostic process in hospital is manpower, while if one considers an outsourcing model the most important criteria is costs and the most important computational and bioinformatics requirements are with regard to data safety and security and networking capabilities.

Part I of the study focused on mapping criteria (6 main criteria and 25 sub-criteria) across different operational models for implementing WGS. A previous systematic review of 147

studies in a related field (human genomics) found 23 challenges linked to the clinical implementation of Whole-exome sequencing (WES) [55], however it was mainly focused on the clinical aspects of the technology and not on the operational aspects. Similarly, a systematic review of 36 studies that delineated evidence of economic evaluation of WES and WGS [56] was focused only on the economic aspects of implementing these technologies without addressing the different components of costs separately (e.g. manpower costs or computational costs) and without addressing other operational criteria. Thus, our systematic review provided a unique and comprehensive perspective with regard to the criteria associated with the implementation of this technology across different operational models. Whereas we focused only on microbiology, our approach may be adopted for studying the technology in other medical disciplines.

Different criteria may influence the decision to implement WGS differently and depend on the advantages and disadvantages of each operational model. It appears that the most significant advantage of adopting an in-house model was the fast TAT [44, 57, 58] and the capability to adjust the test to specific goals [38]. The direct relationship between wet and dry laboratory personnel and between those and the clinicians are expected to enhance the quality of the diagnosis and improve the capability to interpret the results [38, 44]. It was stressed that using outsourced services for clinical decisions should be carefully considered, due to the expected increase in TAT, especially for serious decisions such as tailoring of antibiotic treatment for complex infections [57]. However, the most significant advantages of adopting an outsourced model is that it does not require significant capital and operational investment in a complex and dynamic technological area, as well as provision of ongoing training programs to the laboratory personnel [17], which would potentially facilitate the engagement of new WGS users and eliminate barriers [47]. These advantages may be mostly influential on the decision of small hospitals to adopt this technology [41,42]. We summarized the differences and similarities in the implications of each criteria and sub-criteria while adopting full in-house vs. full outsourcing model for the implementation of WGS, from the point of view of a local hospital laboratory (for details please see Table 1, p. 1092 in [37]).

Part II of our study was targeted in interviewing managers of hospital labs, of public health labs or of infectious diseases units, in order to articulate criteria and operational models for implementing WGS. Most of the interviewees thought that, especially for early stages of WGS implementations, WGS should be fully outsourced, as was stressed by a

previous survey [17]. This approach is more appropriate for retrospective outbreak investigations and non-urgent surveillance, and by batching samples, cost would drop to less than the costs of currently available methods [17]. Additionally, interviewees thought that after solving existing manpower barriers, an in-house model will be the leading choice for performing the analysis stage. In addition, the majority of our interviewees mentioned one central unit, which harbors both sequencing and bioinformatics services, is a better solution for implementing WGS [42] especially for a small country like Israel. All interviewees agreed that choosing the right operational model depends on test goal [47]. The clinical utility of WGS should be clearly defined and demonstrated in order to decide whether to implement WGS or not. Still, similar to our results in Part III, other concerns such as costs, which was the leading concern, as well as requirements for expertise in the 'wet' and 'dry' lab components and QC measurements, would strongly affect the decision [17,47, 55, 58, 59]. Clinical benefits and costs of sequencing [52], as well as evidence that this diagnostic approach is cost-effective [56], were previously demonstrated, yet, more evidence, specifically such that is coming out of the local Israeli health system is warranted.

We found that as compared to participants with limited experience, participants with vast experience with WGS, ranked manpower requirements as less influential on the decision to integrate WGS, when both sequencing and analysis are conducted in-house. We assume that those who have experience (that sequence above 100 samples annually), or those who have accessibility to sequencing and data analysis, do not perceive manpower as a great barrier for implementation since they have their capabilities and face other salient barriers for implementing WGS. Geskin et al. conducted a survey among researchers which were stratified to current users of NGS, future users (not currently using but planning to use it in the next 2 years) and non-users (not currently using it and are not planning to use it in the next 2 years). The first group may resemble (yet not identical) our group of participants with vast experience, while the two last group may resemble our group of participants with limited experience. Roughly a third (31%) of the entire cohort (no between-group distinction was reported) cited the lack of expertise and person time as the leading obstacle for analyzing data. Nevertheless, there was no indication regarding which operational model was conducted. Additionally, 33% of current users and 24% of future users cited that a common obstacle to sequencing was cost (no inferential statistics were reported) [47], however, our results demonstrated no significant

difference in the ranking of the cost criteria among both groups. It was also found in our survey that participant with vast experience with WGS ranked test goal as more influential on the decision to implement WGS (with borderline significant), when sequencing and analysis were conducted in-house. However, it should be noted that we found no association between participants‘ experience and the ranking of test goal criterion when sequencing is conducted in-house and the analysis is outsourced. These mixed results highlight the need for further comprehensive survey among participants with different levels of experience with WGS.

Our multivariable analysis unexpectedly and not according to the reviewed literature, revealed that there was no significant difference in the ranking of criteria (e.g. manpower, cost, computational and bioinformatics, laboratory infrastructure, motivations and test goal) between the different operational models. Apparently, as was already stressed, further comprehensive survey is warranted to verify these results.

Our study has several limitations relating to study selection and inclusion methodology. First, our systematic review was limited to English-language publications and it is possible that there are other criteria that influence the decision to implement WGS published in other languages. Second, we identified criteria and sub-criteria for this decision in publications that had other primary objectives. Thus, these criteria were sometimes only mentioned or briefly discussed in text, while sometimes in-depth discussion was provided. This diversity made the extraction process difficult, and could have led to omission of additional criteria. Additionally, WGS technology is rapidly evolving and thus additional challenges for its implementation may emerge, especially when other applications, such as clinical metagenomics will be discussed in the future. Finally, the sample size achieved in our survey and the distribution of participants' rankings make it difficult to generalize the results to the general population of experts in the field. The limited sample size might stem from the assumed heavy cognitive load of the questionnaire, especially by participants with limited or no experience with WGS. Further research that will reach higher response rate is warranted in order to draw conclusions with regard to the prioritization of the criteria and sub-criteria across the different operational models.

7. POLICY IMPLICATIONS AND RECOMMENDATIONS

Notwithstanding these limitations, our study comprehensively delineated for the first time, the different criteria and sub-criteria for the implementation of WGS in infectious disease diagnostics in hospital settings, across different operational models, and provided results

with regard to their prioritization among decision makers in this field. Taken together, microbiologists and laboratory managers, infectious disease specialists and infection control practitioners, already understand the importance of taking the leap toward WGS since it constitutes a bridge between traditional sequencing method and future approaches such as clinical metagenomics. Microbiological laboratories should understand the importance of WGS in paving the way toward enhanced diagnosis, treatment and disease management and invest in the implementation of this technological gift, making sure they would be able to implement future NGS applications. In order to do so, different viewpoints, priorities, constraints and capabilities should be fully addressed by decision makers. Our suggested eight-criteria weights are a managerial tool that provide the relative importance of these criteria and sub-criteria and thus can guide decision makers with regard to the feasible implementation of WGS in their organizational context, thus effectively implement this technology in the clinical routine. Further research should validate the results of our study using real-world decisions to implement the technology.

8. REFERENCES

(1) Davies SC. Annual Report of the Chief Medical Officer, Volume Two, 2011, Infections and the rise of antimicrobial resistance. London: Department of Health; 2013. Available at: http://media.dh.gov.uk/network/357/files/2013/03/CMO-Annual-Report-Volume-2-20111.pdf Accessed on April 15, 2017.

(2) Luheshi L, Raza S, Moorthie S, Hall A, Blackburn L, Rands C, Sagoo G, Chowdhury S, Kroese M, Burton H. Pathogen genomics into practice PHG Foundation. 2015. Available at: http://www.phgfoundation.org/file/16848/ Accessed on April 15, 2017.

(3) Tang P, Gardy JL. Stopping outbreaks with real-time genomic epidemiology. Genome Med 2014;6(11):104.

(4) Motro Y, Moran-Gilad J. Next-generation sequencing applications in clinical bacteriology. Biomol Detect Quantif 2017;14:1-6.

(5) Grad YH, Lipsitch M. Epidemiologic data and pathogen genome sequences: a powerful synergy for public health. Genome Biol 2014;15(11):538.

(6) Patel R. New developments in clinical bacteriology laboratories. Mayo Clin Proc 2016;91(10):1448-1459.

(7) Moran-Gilad J. How do advanced diagnostics support public health policy development? Euro Surveill 2019;24(4): doi: 10.2807/1560-7917.ES.2019.24.4.1900068.

(8) Forbes JD, Knox NC, Ronholm J, Pagotto F, Reimer A. Metagenomics: the next culture-independent game changer. Front Microbiol 2017;8:1069

(9) Moran-Gilad J, Sintchenko V, Pedersen SK, Wolfgang WJ, Pettengill J, Strain E, et al. Proficiency testing for bacterial whole genome sequencing: an end-user survey of current capabilities, requirements and priorities. BMC Infect Dis 2015;15(1):174.

(10) Schurch AC, van Schaik W. Challenges and opportunities for whole-genome sequencing-based surveillance of antibiotic resistance. Ann N Y Acad Sci 2017;1388(1):108-120.

(11) Rabaa M, Tue N, Phuc T, Carrique-Mas J, Saylors K, Cotten M, et al. The Vietnam initiative on zoonotic infections (VIZIONS): a strategic approach to studying emerging zoonotic infectious diseases. EcoHealth 2015;12(4):726-735.

(12) Lefterova MI, Suarez CJ, Banaei N, Pinsky BA. Next-generation sequencing for infectious disease diagnosis and management: a report of the association for molecular pathology. J Mol Diagn 2015;17(6):623-634.

(13) Cimmino T, Le Page S, Raoult D, Rolain JM. Contemporary challenges and opportunities in the diagnosis and outbreak detection of multidrug-resistant infectious disease. Expert Rev Mol Diagn 2016;16(11):1163-1175.

(14) Nadon C, Walle IV, Gerner-Smidt P, Campos J, Chinen I, Concepcion-Acevedo J, et al. PulseNet International: vision for the implementation of whole genome sequencing (WGS) for

global foodborne disease surveillance. Euro Surveill 2017;22(23): 30544.

(15) Burkholder WF, Newell EW, Poidinger M, Chen S, Fink K. Deep sequencing in infectious diseases: immune and pathogen repertoires for the improvement of patient outcomes. Front Immunol 2017;8:593.

(16) Perez-Losada M, Arenas M. Microbial sequence typing in the genomic era. Infect Genet Evol 2018; 63:346-359.

(17) Kwong JC, McCallum N, Sintchenko V, Howden BP. Whole genome sequencing in clinical and public health microbiology. Pathology 2015;47(3):199-210.

(18) Lavezzo E, Barzon L, Toppo S, Palù G. Third generation sequencing technologies applied to diagnostic microbiology: benefits and challenges in applications and data analysis. Expert Rev Mol Diagno 2016;16(9):1011-1023.

(19) Long SW, Williams D, Valson C, Cantu CC, Cernoch P, Musser JM, et al. A genomic day in the life of a clinical microbiology laboratory. J Clin Microbiol 2013;51(4):1272-1277.

(20) Haller S, Eller C, Hermes J, Kaase M, Steglich M, Radonic A, et al. What caused the outbreak of ESBL-producing Klebsiella pneumoniae in a neonatal intensive care unit, Germany 2009 to 2012? Reconstructing transmission with epidemiological analysis and whole-genome sequencing. BMJ Open 2015;5(5):e007397.

(21) Kaiser T, Finstermeier K, Hantzsch M, Faucheux S, et al. Stalking a lethal superbug by whole genome sequencing and phylogenetics: Influence on unraveling a major hospital outbreak of carbapenem-resistant Klebsiella pneumonia. Am J Infect Control 2018; 46(1):54-59.

(22) Tang P, Croxen MA, Hasan MR, Hsiao WW, Hoang LM. Infection control in the new age of genomic epidemiology. Am J Infect Control 2017;45(2):170-179.

(23) Jackson BR, Tarr C, Strain E, Jackson KA, Conrad A, Carleton H, et al. Implementation of nationwide real-time whole-genome sequencing to enhance listeriosis outbreak detection and investigation. Clin Infect Dis 2016;63(3):380-386.

(24) Sabat AJ, Budimir A, Nashev D, Sa-Leao R, van Dijl J, Laurent F, et al. Overview of molecular typing methods for outbreak detection and epidemiological surveillance. Euro Surveill 2013;18(4):20380.

(25) Sherry NL, Porter JL, Seemann T, Watkins A, Stinear TP, Howden BP. Outbreak investigation using high-throughput genome sequencing within a diagnostic microbiology laboratory. J Clin Microbiol 2013;51(5):1396-1401.

(26) Koser CU, Holden MT, Ellington MJ, Cartwright EJ, Brown NM, Ogilvy-Stuart AL, et al. Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. N Engl J Med 2012;366(24):2267-2275.

(27) Kumar N, Miyajima F, He M, Roberts P, Swale A, Ellison L, et al. Genome-based infection tracking reveals dynamics of clostridium difficile transmission and disease recurrence. Clin Infect Dis 2016;62(6):746-752.

(28) Jiang Y, Wei Z, Wang Y, Hua X, Feng Y, Yu Y. Tracking a hospital outbreak of KPC-producing ST11 Klebsiella pneumoniae with whole genome sequencing. Clin Microbiol Infect 2015;21(11):1001-1007.

(29) Kluytmans-van den Bergh, Marjolein F Q, Rossen JWA, Bruijning-Verhagen PCJ, Bonten MJM, Frieich AW, Vandenbroucke-Grauls, Christina M J E, et al. Whole-genome multilocus sequence typing of extended-spectrum-beta-lactamase-producing Enterobacteriaceae. J Clin Microbiol 2016;54(12):2919-2927.

(30) Nielsen KL, Stegger M, Kiil K, Godfrey PA, Feldgarden M, Lilje B, et al. Whole-genome comparison of urinary pathogenic Escherichia coli and faecal isolates of UTI patients and healthy controls. Int J Med Microbiol 2017;307(8):497-507.

(31) Stojanov M, Magalhaes B, Terletsky V, Basset P, Prod'hom G, Greub G, et al. Development and evaluation of double locus sequence typing for molecular epidemiological investigations of Clostridium difficile. Eur J Clin Microbiol Infect Dis 2016;35(2):175-181.

(32) Roach DJ, Burton JN, Lee C, Stackhouse B, Butler-Wu SM, Cookson BT, et al. A year of infection in the intensive care unit: Prospective whole genome sequencing of bacterial clinical isolates reveals cryptic transmissions and novel microbiota. PLoS Genet 2017;13(4): e1006724.

(33) Ellington MJ, Ekelund O, Aarestrup FM, Canton R, Doumith M, Giske C, et al. The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee. Clin Microbiol Infect 2017;23(1):2-22.

(34) Saaty TL. Decision making with the analytic hierarchy process. Int. J. Services Sciences. 2008; 1(1): 83-97.

(35) Rossetti M, Selandari F. Multi-objective analysis of hospital delivery systems. Comput Ind Eng. 2001;41(3):309-33.

(36) Ahmadi H, Nilashi M, Ibrahim O. Organizational decision to adopt hospital information system: an empirical investigation in the case of Malaysian public hospitals. Int J Med Inform. 2015;84(3):166-88.

(37) Mintzer V, Moran-Gilad J, Simon-Tuval T. Operational models and criteria for incorporating microbial whole genome sequencing in hospital microbiology – A systematic literature review. Clin Microbiol Infect 2019; 25(9):1086-1095.

(38) Arnold C. Considerations in centralizing whole genome sequencing for microbiology in a public health setting. Expert Rev Mol Diagn 2016;16(6):619-621.

(39) Lesho E, Clifford R, Onmus-Leone F, Appalla L, Snesrud E, Kwak Y, et al. The challenges of implementing next generation sequencing across a large healthcare system, and the molecular epidemiology and antibiotic susceptibilities of Carbapenemase-producing bacteria in the healthcare system of the U.S. Department of Defense. PLoS One 2016;11(5):e0155770.

(40) Costa S, Regier DA, Meissner B, Cromwell I, Ben-Neriah S, Chavez E, et al. A time-and-motion approach to micro-costing of high-throughput genomic assays. Curr Oncol 2016;23(5):304-313.

(41) Fricke WF, Rasko DA. Bacterial genome sequencing in the clinic: bioinformatic challenges and solutions. Nat Rev Genet 2014 Jan;15(1):49-55.

(42) Cabibbe AM, Trovato A, De Filippo MR, Ghodousi A, Rindi L, Garzelli C, et al. Countrywide implementation of whole genome sequencing: an opportunity to improve tuberculosis management, surveillance and contact tracing in low incidence countries. Eur Respir J 2018;51(6):1800387.

(43) Davis-Turak J, Courtney SM, Hazard ES, Glen WB, da Silveira WA, Wesselman T, et al. Genomics pipelines and data integration: challenges and opportunities in the research setting. Expert Rev Mol Diag 2017;17(3):225-237.

(44) Peacock SJ, Parkhill J, Brown NM. Changing the paradigm for hospital outbreak detection by leading with genomic surveillance of nosocomial pathogens. Microbiology 2018;164(10):1213-1219.

(45) Cheung MK, Kwan HS. Fighting outbreaks with bacterial genomics: case review and workflow proposal. Public Health Genomics 2012;15(6):341-351.

(46) Pankhurst LJ, Del Ojo Elias C, Votintseva AA, Walker TM, Cole K, Davies J, et al. Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study. Lancet Respir med 2016;4(1):49-58.

(47) Geskin A, Legowski E, Chakka A, Chandran UR, Barmada MM, LaFramboise WA, et al. Needs assessment for research use of high-throughput sequencing at a large academic medical center. PloS one 2015;10(6): e0131166.

(48) Revez J, Espinosa L, Albiger B, Leitmeyer KC, Struelens MJ, ECDC National Microbiology Focal Points and Experts Group. Survey on the use of whole-genome sequencing for infectious diseases surveillance: rapid expansion of European national capacities, 2015-2016. Front Public Health 2017;5:347.

(49) Price J, Gordon NC, Crook D, Llewelyn M, Paul J. The usefulness of whole genome sequencing in the management of Staphylococcus aureus infections. Clin Microbiol Infect 2013;19(9):784-789.

(50) Salipante SJ, ,SenGupta DJ, Cummings LA, Land TA, Hoogestraat DR, Cookson BT. Application of whole-genome sequencing for bacterial strain typing in molecular epidemiology. J Clin Microbiol 2015;53(4):1072–1079.

(51) Raven K, Blane B, Churcher C, Parkhill J, Peacock SJ. Are commercial providers a viable option for clinical bacterial sequencing? Microb Genom 2018: doi: 10.1099/mgen.0.000173.

(52) Farnaes L, Hildreth A, Sweeney NM, Clark MM, Chowdhury S, Nahas S, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med 2018;3:10.

(53) Hayeems RZ, Bhawra J, Tsiplova K, Meyn MS, Monfared N, Bowdin S, et al. Care and cost consequences of pediatric whole genome sequencing compared to chromosome microarray. Eur J Hum Genet 2017;25(12):1303-1312.

(54) Jensen SO, van Hal SJ. Personalized medicine and infectious disease management. Trends Microbiol. 2017;25(11):875-876.

(55) Bertier G, Hetu M, Joly Y. Unsolved challenges of clinical whole-exome sequencing: A systematic literature review of end-users' views. BMC Med Genomics. 2016;9(1):52.

(56) Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med. 2018;20(10):1122-1130.

(57) Yachison CA, Yoshida A, Robertson J, Nash JHE, Kruczkiewicz P, Taboada EN, et al. The validation and implications of using whole genome sequencing as a replacement for traditional serotyping for a national Salmonella reference laboratory. Front Microbiol 2017;8:1044.

(58) Rossen JWA, Friedrich AW, Moran-Gilad J, ESCMID Study Group for Genomic and Molecular Diagnostics (ESGMD). Practical issues in implementing whole-genome-sequencing in routine diagnostic microbiology. Clin Microbiol Infect 2018;24(4):355-360.

(59) Wilson BJ, Miller FA, Rousseau F. Controversy and debate on clinical genomics sequencing-paper 1: Genomics is not exceptional: Rigorous evaluations are necessary for clinical applications of genomic sequencing. J Clin Epidemiol. 2017;92:4-6.