Using the Sankey diagram to visualize article features on the topics of whole-exome sequencing (WES) and whole-genome sequencing (WGS) since 2012

Bibliometric analysis

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Abstract

Background: Sequencing technologies, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), have been increasingly applied to medical research in recent years. Which countries, journals, and institutes (called entities) contributed most to the fields (WES/WGS) remains unknown. Temporal bar graphs (TBGs) are frequently used in trend analysis of publications. However, how to draw the TBG on the Sankey diagram is not well understood in bibliometrics. We thus aimed to investigate the evolution of article entities in the WES/WGS fields using publication-based TBGs and compare the individual research achievements (IRAs) among entities.

Methods: A total of 3599 abstracts downloaded from icite analysis were matched to entities, including article identity numbers, citations, publication years, journals, affiliated countries/regions of origin, and medical subject headings (MeSH terms) in PubMed on March 12, 2022. The relative citation ratio (RCR) was extracted from icite analysis to compute the hT index (denoting the IRA, taking both publications and citations into account) for each entity in the years between 2012 and 2021. Three types of visualizations were applied to display the trends of publications (e.g., choropleth maps and the enhanced TBGs) and IRAs (e.g., the flowchart on the Sankey diagram) for article entities in WES/WGS.

Results: We observed that the 3 countries (the US, China, and the UK) occupied most articles in the WES/WGS fields since 2012, the 3 entities (i.e., top 5 journals, research institutes, and MeSH terms) were demonstrated on the enhanced TBGs, the top 2 MeSH terms were genetics and methods in WES and WGS, and the IRAs of 6 article entities with their hT-indices were succinctly and simultaneously displayed on a single Sankey diagram that was never launched in bibliographical studies.

Conclusion: The number of WES/WGS-related articles has dramatically increased since 2017. TBGs, particularly with hTs on the Sankey, are recommended for research on a topic (or in a discipline) to compare trends of publications and IRAs for entities in future bibliographical studies.

Abbreviations: BS = burst strength, IRA = individual research achievement, MeSH = medical subject heading, NICU = neonatal intensive care unit, RCR = relative citation ratio, TBG = temporal bar graphs, WES = whole exome sequencing, WGS = whole genome sequencing.

Keywords: choropleth map, hT index, research achievement, Sankey diagram, temporal bar graph, whole-exome sequencing, whole-genome sequencing

1. Introduction

The incorporation of sequencing techniques has been rapidly launched into health care,[1] partially attributed to the decreasing costs and clinical utility experience given to clinical settings and some to whole-exome sequencing (WES) and whole-genome sequencing (WGS), which are anticipated to replace conventional genetic tests, such as gene panels and chromosomal microarray analysis.[2]

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All data are publicly available in the PubMed library. The datasets generated during and/or analyzed during the current study are publicly available. All data used in this study are available in Supplemental Digital Content.

Supplemental Digital Content is available for this article.

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Key Points

- We introduced the merit of a Sankey diagram that combines the traditional temporal bar graphs (TBGs) used in bibliometrics.
- TBGs with hot spots and burst strengths were rarely seen in traditional TBGs.
- This paper focuses on the importance of research achievements, such as the impact factor, which cannot be determined solely by the number of publications, and shows how Sankey diagrams can be used and drawn for readers who are interested in bibliometric analysis.

1.1. Advanced techniques in WES and WGS

An increase in the application of sequencing techniques (either exome or genome) has significantly influenced clinical practices and pharmacogenetics. While the genetic disease is suspected in over 50% of the children who are admitted to neonatal intensive care units (NICUs) and die during the first year of life, diagnosis is confirmed in only 20% to 30% of cases, often postmortem.[1,4] As such, multiple factors hinder genetic diagnosis in neonates, including genetic heterogeneity. The disease tends to progress faster in neonates than in other stages of life.[1]

Technological advances in gene sequencing have enabled the rapid reading of any part of the genome at an affordable price.[5,6] NICUs are a key target for the implementation of genomic tools.[7,8] Timely and specific diagnosis of newborns can have critical implications for health and wellbeing for the remainder of an infant’s life.[1]

In contrast to traditional molecular diagnostic methods, WES, especially trio-WES (both parents and their affected child sequenced simultaneously), was approved to be associated with a higher molecular diagnostic yield.[9,10] Broaden diagnostic yield is critical in diagnosing patients with atypical phenotypes, complex phenotypes, or disease-associated hallmark features not yet manifested. Nonetheless, WES does not typically detect intronic variants, trinucleotide repeat expansions, and methylation abnormalities, as well as limited detection of copy-number variants.[9,10] These limitations must be overcome through the WGS technique, which provides coverage of both array and exome targets and further coverage of nonexome regions of the genome.[11]

1.2. Research and publications related to WES and WGS

Unfortunately, as WGS is not as universally pervasive as WES, the reason might be the higher cost and more complex bioinformatics analysis from relevant professionals and qualified lab services required in clinical medicine. However, the issue of financial affordability can be overcome via technique advancement, while numerous WES/WGS-related articles have been published since 2016[12] to address the feasibility and promise of WGS in the foreseeable future.

Which article entities (e.g., publication years, journals, affiliated countries/regions/institutes of origin, document type, and medical subject headings, namely, MeSH terms) contributed most to the fields of WES/WGS is still unknown. We are thus motivated to conduct the bibliometric analysis of articles for a better understanding of the network characteristics of articles on WES/WGS.

1.3. Challenges encountered in bibliometrics

Bibliographic articles place more effort on identifying clusters of topics, literature gaps, and academic silos, as well as the most impactful authors and their research.[13] In contrast to meta-analysis and systematic literature review studies, bibliographic literature reviews use more quantitative and statistical methods to analyze feature characteristics, particularly on the trend of publications and the individual research achievements (IRAs) compared in groups.[14]

Although some studies[15–17] applied line charts or temporal bar graphs (TBGs) to display the trend of publications, the drawback is that there is no such essential information about the hot spots and burst strengths (BS) along the charts/graphs provided to readers.[18–20] Furthermore, how to easily and quickly draw the TBG (or the flowchart) has not been addressed in those studies.[18–20] We are thus going to demonstrate the way to draw the TBG using the Sankey flow diagram (Sankey).[21–23]

Additionally, the IRAs[24–28] should be denoted by bibliometric indices (e.g., the h-index[29], x-index[30], g-index[31], or h′-index[32,33]), taking both publications and citations into account instead of the publications alone to represent the IRA (or contribution to academics), as in these studies.[18,27,34,35] Using the bibliometric indices (e.g., the h′-index) to represent the IRA on a single diagram for comparison among groups is required for development.

1.4. Aims of this study

We applied the Sankey to investigate the evolution of article entities in WES/WGS fields using publication-based TBGs and compare the IRAs among entities using the h′-indices shown on the Sankey.

2. Methods

2.1. Data sources

We programmed Microsoft Excel’s Visual Basic for Applications modules to extract abstracts from icite analysis[36] as of March 12, 2022 and matched them to topical entities, such as article identity numbers, citations, publication years, affiliated countries/regions of origin, and medical subject headings (MeSH terms), in PubMed. The search string was defined as the following: (“(((whole[All Fields] OR wholeness[All Fields]) OR wholes*[All Fields]) AND “genome”[MeSH Major Topic]) NOT (“whole*[All Fields] OR “wholeness”[All Fields] OR wholes*[All Fields]) AND “genomic”[MeSH Major Topic]) AND “sequence analysis, dna”[MeSH Major Topic] AND “humans”[MeSH Terms] OR (“whole genome sequencing”[MeSH Major Topic] OR “whole exome sequencing”[MeSH Major Topic]) AND “humans”[MeSH Terms]) AND ((humans[Filter]) AND (2012:2021[pdat])). A total of 3599 abstracts were collected and deposited in Supplemental Digital Content 1, http://links.lww.com/MD/H378.

The relative citation ratios (RCRs) for each article were extracted from the icite analysis, implying that the RCR values measure the scientific influence of each paper by field- and time-adjusting the citations it has received and benchmarking to the median for National Institutes of Health publications.[17]

Ethical approval is not necessary for this study because all the data were obtained via the Internet.

2.2. Three parts divided in this study

Based on the study goals, 3 phrases (i.e., data arrangement in Section 2.1, data analysis, and representation in this section) were divided to achieve the study goals.

2.2.1 Productive countries of articles on WES/WGS

Traditionally, the geographical distribution of countries/regions in publications is applied to bibliographical studies.[24,30,38] In this study, we separately display the distribution of articles on WES and WGS for countries/regions using choropleth maps.
2.2.2. TBGs using the Sankey to draw. Traditionally, TBGs are displayed in rows with identical width bars, each one by one from top to bottom, even if hot spots and BS are marked on the TBGs. The drawback of the traditional TBG is that no such information about data distribution has been displayed over the years. The enhanced TBG is thus proposed to combine the stacked bar chart with the TBG into the Sankey. Four visualizations of the enhanced TBG were made for displaying the comparisons of countries, journals, research institutes, and MeSH terms in publications on WES/WGS.

2.2.3. hTs for entity comparisons in IRAs on the Sankey. The hT index was applied to evaluate the contributions to the fields of WES/WGS for each entity. The most prominent countries/regions with higher hT indices on the topics of WES and WGS were highlighted on the enhanced TBGs.

The hT index based on the RCR is computed by equation 1, where \( j \) is the \( j \)-th article in descending order and \( n \) is the RCRs of an article for an entity. The residual weights in excess and tail citations are presented in equation 2.

\[
\begin{align*}
\text{h-index}_{(top\ j)} &= \frac{j}{2j-1}, \quad n_j \leq j \\
\text{hT}_{(j)} &= h + \text{residual weights} = \frac{j}{2j-1} + \sum_{i=1}^{n} \frac{1}{2i-1}, \quad n_j > j \\
\text{hT} &= \sum_{j=1}^{N} \text{hT}_{(j)},
\end{align*}
\]

Now, if an author, for example, has \( N \) cited articles with associated citations \( n_1, n_2, n_3, \ldots, n_N \) (ranked in descending order), the hT score for any single paper ranked \( j \) in the list (with \( n_j \) RCRs), denoted \( \text{hT}_{(j)} \) in equation 2. The hT-index for the whole list of cited articles is then calculated by summing all weights (allocated in equations 1 and 2) through equation 3. As such, the resulting sum is the hT index. Readers are invited to practice it at the link [39] (e.g., input 10 to obtain 2.13 for a single article with 10 citations, 3.28 for 100 citations, 4.44 for 1000 citations, 5.59 for 10,000 citations, or a vector (e.g.,) RCRs composed of \( \{6,4,2,2,1\} \) in 5 articles to obtain \( \text{hT} = 4.03 \)).

Social network analysis was performed on cowords of entities (e.g., years, countries, institutes, journals, MeSH terms, and document types) in articles. The relation weights between entities were computed based on the 3599 articles. The relationship (denoted by arc) was applied to draw the Sankey for each neighbor entity (called a node in the diagram).

2.3. Tools used in this study

We applied the author-made modules in MS-Excel to arrange and analyze the data. The ways to draw the enhanced TBGs and the hTs comparison among entities using the SankeyNATUC are linked in reference [42].

The pages of hypertext markup language (HTML) used for Google Maps were created for choropleth maps. All relevant information was linked to dashboards on Google Maps. This study flowchart is shown in Figure 1.

3. Results

3.1. Geographical distribution of publications on WES/WGS

The 3 countries (the US, China, and the UK) have occupied most articles in the WES/WGS fields since 2012; see Figure 2.
Readers are invited to scan the QR code in Figure 2 to examine the details about the information on the choropleth maps.

### 3.2. Enhanced TBGs showing the top 5 entities regarding publications on WES/WGS

The 5 countries with the most publications on WES/WGS are shown in Figure 3, including the stacked bar charts on the top and the traditional TBGs on the bottom. Viewing the bottom panel in Figure 3, we can see additional information about the hot spots (denoted by the black bar). The BS (represented by the bar width), and the trend determined by the last 4 years and colored by the trend types [19,20] for increasing, ready to rise, decreasing, and ready to decline using green, yellow, red, and light green colors, respectively, to denote.

The enhanced TBGs are presented in Figures 4–6 for journals, institutes, and MeSH terms, respectively. We can see that the most productive entities (either journals or institutes) have more proportions since 2016, with the feature of traditional stacked bar chart, distinct hot spots (with black areas), BS shown on the right-side hand, and trends with colors at the far right side.

The top 3 MeSH terms are {genetics, methods, diagnosis} and {genetics, methods, genome human} for WES and WGS, respectively. The top 5 terms each year are shown in Figure 6 using the Sankey technique, which is rarely seen in bibliographical studies.

### 3.3. hTs for entity comparisons in IRAs on the Sankey

The hTs for the top 3 entities are shown in Figure 7. One look is worth a thousand words and quite a few numbers, too. [44]

The RAs of 6 article entities with their hT-indices are succinctly and simultaneously displayed on a single Sankey diagram that was never launched in bibliographical studies. Until now, such a picture – the Sankey – we perceived is worth an effort by piecing them into a drawing program, [45] as we demonstrated in Supplemental Digital Content 2, http://links.lww.com/MD/H379.

Additionally, the top 3 elements in each entity are distinctly different from the productive ones in Figures 3–6, particularly in journals (e.g., PLos One and Sci Rep vs E engl J Med and Nature, except Genet Med in WES). We confirmed that only hT (or other bibliometric indices) could be the IRA proxy in lieu of publications, as reported in many bibliographical studies.[24–28]

### 4. Discussion

We observed that the 3 countries (the US, China, and the UK) occupied most articles in the WES/WGS fields since 2012, the 3 entities (i.e., top 5 journals, research institutes, and MeSH terms) were demonstrated on the enhanced TBGs, the top 2 MeSH terms were genetics and methods in WES and WGS, and the RAs of 6 article entities with their hT-indices were succinctly and simultaneously displayed on a single Sankey diagram that stipulated that one look is worth a thousand words.

### 4.1. Additional information

Technological advances in gene sequencing have enabled the rapid reading of any part of the genome at an affordable price.[5,6] NICUs are a key target for the implementation of genomic tools.[7,31] Some studies focused on the use of these WES/WGS...
technologies and conducted in NICU settings have yielded highly promising results. Further advances are required to make precision, personalized, and predictive Medicine into reality.

Although integration and interpretation of the data produced by genomic sequencing is a key obstacle to the incorporation of these strategies into clinical routine practice,

There were 2 major objectives achieved: we applied an enhanced TBG to interpret article entity evolution in WES and WGS, and we could understand the IRAs compared between entities using the hT indices shown on the Sankey. Two studies have applied the Sankey method to bibliometric analysis.

A demonstration and introduction to the 3 Sankey diagrams (e.g., Figs. 5–7) can be found at the following link and Supplemental Digital Content 2, http://links.lww.com/MD/H379. The hT-index (or other bibliometric indicators) are suitable for measuring RAs due to the fact that they take both publications and citations into account. We used the hT index to calculate the RA for entities and demonstrate the Sankey method used in this study as the only index that takes into account all publications (see Eqs. 1 and 2).

Several articles have been published in the literature related to WES/WGS. In spite of this, none of the studies conducted a bibliometric analysis of the topic. The top 3 countries (the US, the UK, and Germany) have higher hTs, which are reflected in the IRAs of their institutions, for example, Baylor College of Medicine (US), University of Oxford (UK), and Harvard Medical School (US).

4.2. Implications and changes

New genomic sequencing techniques have shown considerable promise in neonatology, and they will likely increase diagnostic rates and reduce diagnosis times. The use of WGS for diagnosis of rare disorders in ill neonates in NICUs has been raised as an ethical concern, but it has the potential to augment or modify the care provided to this vulnerable population of patients.

First, the hT-index with decimal places can be used to complement the original h-index in order to improve the discrimination power for identifying the IRAs and rankings of a given group. We suggested using the hT index to present the IRAs in the Sankey and in future bibliographical studies.

The second feature is that the Sankey method was presented as a way of highlighting all-in-one entities in bibliometrics, and has proven to be viable and feasible.
As a third feature, readers can access teaching material at the link[43] and Supplemental Digital Content 2, http://links.lww.com/MD/H379 which will assist them in replicating the relevant studies in the future.

Fourth, some scholars pointed out that while Sankey diagrams are better known, alluvial plots are generally a good deal easier to generate.[63] After viewing the teaching materials[44] and using the software[42] to draw the Sankey diagrams, it is anticipated that more research will apply the Sankey (or alluvial) diagrams to visualize (or dance) their data in the future.

Additionally, citations have been replaced with RCRs.[37] The reason for this is that the RCRs do not depend on the age of the article: older articles earn more citations than younger articles. Based on normalized years and disciplines, RCRs are considered a fair indicator for comparing article impacts.

There is a dedicated software program that can solve the problem of calculating the hT-index even though it is more complex than the h-index in computation. Here is a link[39] that provides the programming codes to understand how the hT-index is calculated within a second.

**Figure 6.** Top 3 observed MeSH terms in WES and WGS since 2012 (Note. Showing names on the diagram, we defined all elements column by column with the flow from 2013 to 2022 for MeSH terms with most frequently observed in years. Terms in 2012 were absent). MeSH = medical subject heading, WES = whole exome sequencing, WGS = whole genome sequencing.

**Figure 7.** Top 3 article entities with hT indices in WES and WGS since 2012 (note. Red curves linked to all entities related to the US; Germany has nothing to link due to no any institute related to Germany in these 3 research institutes; the highest hT is onto the journal articles due to the number of articles more than other entities). WES = whole exome sequencing, WGS = whole genome sequencing.
5. Conclusion

The use of the Sankey diagram to display network characteristics of articles related to WES/WGS led to a breakthrough. With an all-in-one feature involving frequently used entities with hT indices on a Sankey diagram, article space could be reduced, and readers could focus on the fewer influential entities that are important to bibliometrics. In future studies, the Sankey diagram can be applied to bibliometrics on other topics in addition to WES/WGS.

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Author contributions

MJ developed the study, TW and KW analyzed the data. FJL monitored the process of this study and helped respond to the reviewers’ advice and comments. MJ and TW drafted the manuscript, and all authors provided critical revisions for important intellectual content. The study was supervised by FJL. All authors have read and agreed to the published version of the manuscript.

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