The 100 most-cited articles on prenatal diagnosis
A bibliometric analysis
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Abstract
Background: The number of citations a published article receives can be used to demonstrate its impact on a field of study. The objective of this study was to identify and characterize the 100 most-cited research articles (T100) published on prenatal diagnosis.

Methods: The Web of Science (WOS) database was searched for papers on prenatal diagnosis published between 1900 and 2018. The 100 most-cited original articles and reviews were recorded. Each eligible paper was reviewed for authors, journal name, year of publication, country, institution, total citations, citation density, H-index, research field, article type, and keywords.

Results: The T100 were published between 1972 and 2015 with a mean of 332.7 citations per paper (range: 196–1254). Most of the T100 were published between 1990 and 2005, in 35 journals led by New England Journal of Medicine (n = 14) followed by Lancet (n = 10), and Proceedings of the National Academy of Sciences of the United States of America (n = 8). Studies on method application, which promotes field development, were the majority article type. The team of Lo YM featured prominently in the field, and the United States of America, United Kingdom, and Hong Kong, China were the leading countries-regions. Frequency of cooperation was also highest among these 3 regions. Hierarchical cluster analysis produced 4 groups of keywords.

Conclusion: Our analysis provides a historical perspective on scientific progress in prenatal diagnosis and may assist clinicians and researchers in assessing the quality of research over the past 50 years. It also provides concise information to guide future research.

Abbreviations: β-hCG = β-human chorionic gonadotrophin, ISI = Institute for Scientific Information, NIPT = non-invasive prenatal testing, PAPP-A = pregnancy-associated plasma protein-A, PNAS = Proceedings of the National Academy of Sciences, WOS = Web of Science.

Keywords: academic influence, bibliometric analysis, citations, prenatal diagnosis, Web of Science

1. Introduction
Prenatal examination and diagnosis have played an important role in raising the quality of population for nearly 2 centuries. They allow parents to make informed decisions about a pregnancy, healthcare professionals to optimize antenatal care, and families to prepare for the birth of the baby. A large volume of research is published annually giving new insights into the development of safe and valuable prenatal diagnostic techniques.[1-3]

Bibliometrics is a type of statistical and quantitative analysis of the academic impact and characteristics of publications within a research field.[4] Citation analysis is a bibliometric analysis method used to quantify the relative importance of a scientific publication by examining the citations attributed to published research. Although there are obvious disadvantages in assessing the quality of a study simply based on the quantity of citations, it is widely accepted that this is the best method currently available for judging the merit of a paper or a journal.[5] Bibliometric studies have been published in several medical fields, including diabetes,[6] obesity,[7] gastrointestinal medicine,[8] asthma,[9] and coronary heart disease.[10] However, to the best of our knowledge, this type of identification has not been used in the field of prenatal diagnosis, and articles with significant findings that have contributed considerably to the development of antenatal diagnosis have not been identified and summarized comprehensively.

In this study, we aimed to analyze the characteristics of the 100 most-cited articles in antenatal diagnosis (T100) during the last 50 years, from a bibliometric perspective. We also intended to identify factors, such as journal and country/region, that contribute to successful citation.

2. Methodology
The expanded citation index of the database of the Institute for Scientific Information (ISI) Web of Science (WOS) was used to identify the most-cited papers in prenatal diagnosis research between 1900 and July 16, 2018. Searches were conducted on a
The T100 published between 1972 and 2015, identified from 2010-266 published articles and these were listed in descending order of number of citations. The data extraction process was performed independently by 2 reviewers (MLZ and YZ). In cases of discrepancy between the reviewers, consensus was achieved with the help of a third independent reviewer (YFL). The abstract of each search result was read thoroughly to ensure that prenatal diagnosis was the major subject of the research. At last, the 100 most-cited articles were obtained and reviewed.

For the selected 100 articles, the following information was recorded: author names, journal name, country/region of authors, year of publication, institution, total number of citations, H-index of authors, citation density (defined as citations per year after publication), article type, research field, and keywords. Each article was categorized by type as follows:

- (i) studies of method application;
- (ii) observational clinical trials, including prospective/retrospective studies and case reports;
- (iii) molecular level trials, including bench-top laboratory research of clinical samples or research involving animal models;
- (iv) reviews, including literature reviews and meta-analyses;
- (v) epidemiological studies; and
- (vi) guidelines.

Research field was categorized according to study field classification on WOS. Keywords included the author’s keywords, KeyWords Plus, and high frequency words (Articles were read in full and 3–5 high frequency words were summarized according to topic and frequency of occurrence.) To eliminate duplication and improve accuracy, we took synonyms into consideration, for example, “Mutation Screening”, “Genetic Analysis”, and similar terms were classified as “DNA/Genes Analysis”, and “Chromosome Breakpoints”, “Chromosome Deletion”, and similar terms were classified as “Chromosomal Defects”.

BibExcel software (designed by Persson and available at homepage.univie.ac.at/juan.gorraiz/bibexcel/index.html) was used to analyze the text data downloaded from WOS. VosViewer (Leiden University, Leiden, Netherlands) was used to construct co-occurrence networks of important terms (authorship, country/region, and keywords). SPSS 19.0 (SPSS Inc., Chicago, IL) was used for statistical analysis, with Pearson’s correlation coefficient used to determine the relationship between dependent and independent variables. A dendrogram based on morphological traits was plotted using hierarchical cluster analysis and the between-group linkage method. Distance values were computed by dissimilarity cosine, rescaled between 0 and 1. Results were considered significant when \( P < .05 \).

3. Results

3.1. Total citations and citation density

The T100 published between 1972 and 2015, identified from 2010-266 publications, are listed in descending order in Table 1. Total citations for each article ranged from 196 to 1254, and the mean number of citations per article was 332.7. Most of the articles \( (n = 93) \) received more than 200 citations; however, only 11 articles had more than 500. Citation density ranged from 5.0 to 71.7, with a mean density of 20.7. Citation density was positively correlated with total citations (Pearson’s correlation coefficient = 0.511, \( P < .01 \)), with articles with a higher citation density tending to have more total citations. The most cited paper was published in the *Lancet* in 1997,\(^{11}\) an article that first reported that fetal DNA was found in maternal plasma and could be used for non-invasive prenatal diagnosis. The article with the highest citation density was a meta-analysis from 2015\(^ {12} \) reporting that screening for trisomy 21 by analysis of cell-free DNA in maternal blood is superior to traditional screening methods, with higher detection rates and lower false-positive rates.

3.2. Year of publication, article type, and journal

More than 80% of the articles were published after 1990. In terms of article type, method application studies and observational clinical trials contributed the largest proportion (33 and 31 articles, respectively), closely followed by molecular basis studies (24 articles). The total share of reviews, epidemiological studies, and guidelines was a low 12%. Distribution by publication year and article type is shown in Figure 1.

The T100 were published in 35 journals. Table 2 presents the journals that contributed more than 2 articles to the T100, led by *New England Journal of Medicine* \( (n = 14) \) followed by *Lancet* \( (n = 10) \). *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* was third on the list with eight articles. We found a positive correlation between journal impact factor and the number of T100 articles (Pearson’s correlation coefficient = 0.761, \( P < .01 \)), with journals with a higher impact factor tending to have more T100 articles.

3.3. Authorship, country/region, and cooperation networks

A total of 13 authors contributed more than 3 articles to the T100 and were listed as the first author or corresponding author (Table 3). Lo YM authored the most classic papers \( (n = 16) \) followed by Lau TK, who authored 14 classic papers. Lo YM and Nicolaides KH ranked highest as first or corresponding authors, co-authoring 16 and 6 articles, respectively. Nicolaides KH, Lo YM and Cantor CR were the 3 authors with the highest H-index ranking. H-index was not obviously correlated with the number of articles published by these authors \( (P > .05) \). Almost all of the authors in Table 3 are from Hong Kong, China and the United States of America (USA). Networks of author cooperation are documented and their analysis presented visually in Fig. 3A.

The most frequent cooperation was between Lo YM and Lau TK \( (n = 14) \), followed by Lo YM–Leung TN \( (n = 8) \), Lau TK–Leung TN \( (n = 8) \), Lo YM–Chan KC \( (n = 7) \), and Lau TK–Chan KC \( (n = 7) \).

The articles originated from 25 different countries/regions. The USA contributed the most articles \( (n = 58) \), followed by the United Kingdom (UK) \( (n = 29) \), and Hong Kong \( (n = 16) \) (Fig. 2). Bilateral cooperation was most frequent between the USA and UK \( (n = 7) \), followed by the USA and Hong Kong \( (n = 6) \), and the UK and Hong Kong \( (n = 6) \) (Fig. 3B). The UK \( (n = 35) \) and USA \( (n = 31) \) contributed to the majority of bilateral cooperation (Fig. 3B).
3.4. Research fields and keywords

The largest number of studies were in “Medicine, General and Internal” (n=29), and “Obstetrics and Gynecology” (n=17). Additionally, a considerable proportion of research was in “Genetics and Heredity”, “Multidisciplinary Science”, and “Pediatrics”, according to the WOS study field classifications (Table 4).

Table 5 presents a list of the most frequently used (used more than once) T100 keywords. The keyword DNA/Gene Analysis occurred the most (n=59), followed by Peripheral Blood (n=28), Non-invasive Testing (n=27) and Fetal DNA (n=24). The hierarchical clustering results are presented as a dendrogram in Figure 4, and provide insight into the relationships between keywords. The 42 keywords occurring more than twice were classified to 4 clusters. The first cluster included Cystic Fibrosis, Fragile X Syndrome, Congenital Muscular Dystrophy, Thalassemia, and Chromosomal Defects, described as “prenatal diagnosis of diseases associated with chromosomal defects”; the second cluster included Non-invasive Testing, Polymerase Chain Reac-

| Rank | Year | First author | No. of citations | Citation density | New rank |
|------|------|--------------|------------------|------------------|----------|
| 1    | 1997 | Lo YM       | 1254             | 59.71            | 6        |
| 2    | 1996 | Bianchi DW  | 1019             | 50.95            | 8        |
| 3    | 1993 | Noguchi M   | 992              | 39.68            | 10       |
| 4    | 1998 | Lo YM       | 957              | 47.85            | 11       |
| 5    | 1995 | Bianchi DW  | 778              | 35.16            | 12       |
| 6    | 1987 | Kogan SC    | 773              | 24.94            | 13       |
| 7    | 1972 | Brock DJ    | 584              | 12.70            | 15       |
| 8    | 1993 | Chelly J    | 582              | 23.28            | 17       |
| 9    | 1991 | Rousseau F  | 547              | 20.26            | 18       |
| 10   | 2002 | Babkina JL  | 536              | 33.50            | 19       |
| 11   | 2008 | Fan HC      | 503              | 50.30            | 21       |
| 12   | 2011 | Palomaki SE | 494              | 70.57            | 23       |
| 13   | 1991 | Warburton D | 485              | 17.96            | 25       |
| 14   | 2008 | Chong SS    | 440              | 22.00            | 27       |
| 15   | 1992 | Speiser PW  | 397              | 15.27            | 29       |
| 16   | 2012 | Wapner RJ   | 391              | 65.17            | 31       |
| 17   | 1996 | Metkus AP   | 385              | 17.50            | 33       |
| 18   | 2012 | Bianchi DW  | 378              | 63.00            | 35       |
| 19   | 2003 | Driscoll DA | 377              | 15.08            | 37       |
| 20   | 1999 | Wilmels JL  | 376              | 19.79            | 39       |
| 21   | 1999 | Bonnet D   | 376              | 19.79            | 41       |
| 22   | 1998 | Lo YM      | 440              | 22.00            | 43       |
| 23   | 1989 | Rhoads GG   | 350              | 12.07            | 45       |
| 24   | 2011 | Chiu RW    | 346              | 49.43            | 47       |
| 25   | 2001 | Crawford DC | 342              | 20.12            | 49       |
| 26   | 2000 | Toretsky D  | 341              | 20.00            | 51       |
| 27   | 1995 | Yoon BH    | 337              | 14.65            | 53       |
| 28   | 2003 | Belto LUL  | 336              | 22.40            | 55       |
| 29   | 1997 | Kan YM     | 335              | 8.38             | 57       |
| 30   | 1997 | Gale KB    | 324              | 15.43            | 59       |
| 31   | 2004 | Chan KC    | 319              | 22.79            | 61       |
| 32   | 1993 | Hamosh A   | 314              | 12.56            | 63       |
| 33   | 2011 | Ehrich M   | 314              | 44.57            | 65       |
| 34   | 2001 | Cicero S   | 309              | 18.19            | 67       |
| 35   | 2012 | Palomaki SE| 308              | 51.00            | 69       |
| 36   | 2000 | Chong SS   | 306              | 17.00            | 71       |
| 37   | 1991 | Lo YM      | 305              | 15.05            | 73       |
| 38   | 1999 | Grandjean H| 295              | 15.53            | 75       |
| 39   | 1995 | Wang W     | 295              | 12.83            | 77       |
| 40   | 2010 | Lo YM      | 290              | 32.65            | 79       |
| 41   | 1990 | Ransley PG | 289              | 10.32            | 81       |
| 42   | 1997 | Bianchi DW | 287              | 13.67            | 83       |
| 43   | 1995 | Ledbetter DH| 282             | 12.26            | 85       |
| 44   | 1983 | Woo SL     | 274              | 7.83             | 87       |
| 45   | 2003 | Wald NJ    | 273              | 18.20            | 89       |
| 46   | 1990 | Old JM     | 260              | 9.29             | 91       |
tion, Down Syndrome, Trisomy, Aneuploidy, Parallel Shotgun Sequencing, Peripheral Blood, First Trimester, and DNA/Gene Analysis, described as “non-invasive diagnosis via maternal peripheral blood”; the third cluster included HCG, Maternal Age, Fetal Nuchal Translucency, and Ultrasonography, described as “prenatal diagnosis via ultrasonography joint serum indexes and maternal age”; and the fourth cluster included Fetal Surgery, Malformations, and Congenital Heart Disease, described as “fetal therapy of partial congenital malformations”.

4. Discussion

Identification of classic citations can facilitate the recognition of academic advances in a particular discipline, as well as help to identify emerging topics and future directions. The aim of this bibliometric analysis was to provide insight into the development over time and the circumstances of prenatal diagnosis research. The T100 in our study were cited between 196 and 1254 times. This number lags far behind citation classics in asthma studies, (701–2947 citations) and coronary heart disease (1157–7829 citations) during the time periods covered by those studies. Citation rates differ between specialties and depend on the size of the research field. Hotter scientific fields, such as cancer and neurodegenerative disorders tend to have a higher number of classic citations. However, the assessment of classic citations is inherently limited, as citations accumulate over time and recently published articles will be underestimated irrespective of their true impact. Citations gradually reach their peak numbers 3 to 10 years after publication and tend to decrease afterwards. To overcome this limitation, we analyzed citation density. Most of the T100 were published between 1990 and 2005, but the top 5 ranked articles for citation density were focused on the period from 2011 to 2015, indicating an increasing focus on the field of prenatal diagnosis in more recent years and improved availability of resources for research.

Outstanding articles tend to be published in journals with high impact factors, and high impact factor journals facilitate the academic influence of articles. Our results support this. The 3 journals that ranked highest for citations, New England Journal of Medicine, Lancet, and PNAS, have an impact factor of higher than 50 or the peak level in the subspecialty. Most of the highly cited articles were studies of method application, which suggests that prenatal diagnostic and screening options are rapidly increasing, largely pushed by technological advances. Several methodologies for performing reliable prenatal diagnostic testing, ranging from basic biomolecular methods (qPCR, QF-PCR, COLD-PCR coupled with Sanger sequencing and MEMO qPCR) to highly sophisticated and costly methodology, such as MALDI-TOF mass spectrometry, array primer single-base extension, and PCR/LDR/capillary electrophoresis, have been documented in the literature. Similarly, the large majority of the T100 in the field of imaging have been relatively recently published “methods-type” articles. Our findings also revealed that high quality observational clinical trials and molecular-based research gave impetus to the development of prenatal diagnosis.

The majority of our T100 originated from developed countries in Europe and North America; the voice from Asia, Africa, and South America was relatively quiet. The USA ranked highest for quality of scientific production in prenatal diagnosis research,
followed by the UK and Hong Kong, and the frequency of cooperation among these 3 country/regions was also highest. The visualization of our geographic analysis clearly showed a regional imbalance in development in this field. A similar phenomenon is apparent in other fields, including gastrointestinal medicine,
asthma,
and coronary heart disease.
Biomedical research productivity is largely dependent on a country's per capita gross national product, which influences the funding allocated for research and development.

Gains in quality of life and survival made through improved prenatal examination and diagnosis have yet to reach globally.

Lo YM and team made the important discovery of free fetal DNA in the maternal circulation in 1997, creating a precedent for non-invasive prenatal testing (NIPT). They featured prominently in our T100, with further work published in 2003 and 2007 demonstrating that the placenta is the main source of fetal RNA in maternal plasma and that fetal RNA in maternal plasma could be used for detection of Down syndrome with over 90% accuracy.
The use of NIPT potential avoids or reduces the need for invasive techniques, such as chorionic villus sampling and amniocentesis. Although Lo YM’s discovery of free fetal DNA in the maternal peripheral blood was more than 2 decades ago, the transfer of NIPT from research into clinical practice has been rather fragmented. Despite advances in the translation of methods, a lack of sensitivity and low reproducibility in distinguishing between fetal and maternal sequences remain challenges.

Moreover, the techniques are cumbersome and prone to contamination, presenting a conspicuous dependence on the handling expertise of the technicians. Thus, NIPT has yet to be routinely applied in clinical diagnostics and the detection of genetic diseases. More than 60 years since its application to obstetrics, ultrasonography has played important roles in modern prenatal care, including assessment of gestation age, fetal viability, multiple pregnancy, placental location, fetal morphology and growth. After entering the 1990s, screening for aneuploidies has focused on the first trimester of pregnancy.

Which is an algorithm based on the combination of maternal age, fetal nuchal translucency thickness and maternal serum indexes including free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A).

In the last decade, several additional sonographic markers have been described that improve the detection rate of malformations and

### Table 3

| Author       | No. of articles | No. of first or corresponding authors | H-index | Affiliation                                  | Country/region   |
|--------------|-----------------|--------------------------------------|---------|---------------------------------------------|------------------|
| Lo YM        | 16              | 16                                   | 82      | Chinese University of Hong Kong             | Hong Kong, China |
| Lau TK       | 14              | 0                                    | 54      | Chinese University of Hong Kong             | Hong Kong, China |
| Chu RW       | 11              | 4                                    | 50      | Chinese University of Hong Kong             | Hong Kong, China |
| Nicolaides KH| 10              | 6                                    | 105     | King's College School of Medicine           | UK               |
| Leung TN     | 8               | 0                                    | 39      | Chinese University of Hong Kong             | Hong Kong, China |
| Chan KC      | 7               | 2                                    | 43      | Chinese University of Hong Kong             | Hong Kong, China |
| Harrison MR  | 6               | 3                                    | 81      | University of California                    | USA              |
| Leung TY     | 6               | 0                                    | 37      | Chinese University of Hong Kong             | Hong Kong, China |
| Lun FM       | 5               | 1                                    | 13      | Chinese University of Hong Kong             | Hong Kong, China |
| Cantor CR    | 5               | 2                                    | 82      | University of Boston                         | USA              |
| Adzick NS    | 4               | 4                                    | 76      | University of California /Children’s Hospital of Philadelphia | USA |
| Bianchi DW   | 4               | 4                                    | 57      | Harvard Medical School/Tufts University School of Medicine, | USA |
| Tsui NB      | 4               | 1                                    | 21      | Chinese University of Hong Kong             | Hong Kong, China |

Figure 2. Geographical distribution of countries/regions in 100 top-cited papers.
reduce the false-positive rate.\textsuperscript{[2]} Fetal therapy has tremendous potential to treat a broad range of congenital disorders. The goal of fetal therapy is to provide the best possible outcome for the fetus, while minimizing the risk to the mother.\textsuperscript{[30]} Fetal therapy is not just restricted to the correction of structural anomalies—prenatal stem cell transplantation and gene therapy enjoy a brighter prospect for abnormal genetic conditions.\textsuperscript{[31]} There is still a need for ongoing research to develop novel methods and improve specificity and safety.

Our study has several limitations. First, we confined the search to English language journals and did not include citation counts from PubMed, Scopus, or Google Scholar. Second, inherent bias exists in citation analysis.\textsuperscript{[32]} The total numbers of article citations accumulate over time, meaning that older publications will have received more citations than new ones. Authors are more likely to cite articles in their own language, and English articles are more likely to be cited overall. Third, the possibility of oriented or biased citing, including self-citation, in-house, or negative citation, cannot be ignored. Lastly, bibliometric analysis may omit some publications of high quality or that deserve scientific merit.

5. Conclusion

Although bibliometric analysis has its limitations, it provides an important quantitative method for comparing research in scientific fields. To our knowledge, this study is the first report on the 100 most-cited papers in prenatal diagnosis. It highlights the landmark contributions leading to developments of prenatal diagnosis.

| Table 4 | Research fields of the 100 most-cited articles. |
|---------|-----------------------------------------------|
| Research field | No. of articles |
| Medicine, general and internal medicine | 29 |
| Obstetrics and gynecology | 17 |
| Genetics and heredity | 16 |
| Multidisciplinary sciences | 10 |
| Pediatrics | 9 |
| Acoustics | 6 |
| Medical laboratory technology | 6 |
| Radiology, nuclear medicine, and medical imaging | 6 |
| Surgery | 5 |
| Cell biology | 4 |
| Biochemistry and molecular biology | 4 |
| Medicine, research and experimental | 4 |
| Hematology | 4 |
| Cardiac and cardiovascular systems | 3 |
| Peripheral vascular disease | 3 |
| Urology and nephrology | 1 |
| Public, environmental and occupational health | 1 |
| Reproductive biology | 1 |

| Table 5 | Keywords occurring more than once in the 100 most-cited articles. |
|---------|---------------------------------------------------------------|
| Keywords | Frequency | Keywords | Frequency |
| DNA/gene analysis | 59 | HCG | 3 |
| Peripheral blood | 28 | Malformations | 3 |
| Non-invasive Testing | 27 | Cystic fibrosis | 3 |
| Fetal DNA | 24 | Fetal surgery | 3 |
| Ultrasonography | 20 | Cytokines | 2 |
| Chromosomal Defects | 20 | Detection rate | 2 |
| Down syndrome | 14 | Invasive testing | 2 |
| First trimester | 13 | Intra-amniotic Inflammation | 2 |
| Polymerase chain reaction | 12 | Pediatrics | 2 |
| Trisomy | 10 | Fmr1 | 2 |
| Aneuploidy | 9 | False-positive rate | 2 |
| Fetal nuchal translucency | 7 | Epidemiology | 2 |
| Thalassemia | 7 | Molecular basis | 2 |
| Congenital heart disease | 6 | Fetal RhD status | 2 |
| Congenital diaphragmatic hernia | 5 | Fetal infection | 2 |
| Aneuploidy | 4 | Second trimester | 2 |
| Fragile X Syndrome | 4 | Clinical validation | 2 |
| Karyotype | 3 | Chorionic villus sampling | 2 |
| Parallel shotgun sequencing | 3 | Amplification reaction | 2 |
| Maternal age | 3 | Chronic villus sampling | 2 |
| Congenital muscular dystrophy | 3 | Acute leukemia | 2 |
diagnosis, and is instructive for researchers who are new to the
field. The results of this report emphasize the quality of prior
research of prenatal diagnosis and could stimulate new
approaches and thoughts. Additionally, it provides a historical
perspective on progress in prenatal diagnosis research and serves
as a source for future academic pursuit.

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Figure 4. Hierarchical clustering of keywords occurring more than twice in the 100 most-cited papers.
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