Mapping Publication Trends and Knowledge Structure on Non-Invasive Prenatal Testing – A Bibliometric Analysis

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Research

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Abstract

Background: Non-invasive prenatal testing (NIPT) has become the widely adopted prenatal testing for screening the common aneuploidy of pregnant woman and even extended to detecting copy number variations (CNVs) and Monogenic disease. In recent 10 years, NIPT has become an increasingly important scholarly focus. However, data on long-term bibliometric studies on NIPT has not been reported.

Objective: The purpose of this study was to map publications trends and to explore the knowledge structure on NIPT.

Methods: Publications were collected from database PubMed in the past 10 years. A bibliometric analysis based on PubMed was conducted to investigate the publication trends and the knowledge structure. Co-word clustering analysis and strategic diagram of highly frequent major MeSH terms were utilized to detect the hot spots in this field.

Results: A total of 2160 articles about NIPT were retrieved according to our search strategy in this study. Article was the main document type. The 10 most active journals published 29.3% (633/2160) of the publications in this area. By analyzing and summarizing the highly frequent major MeSH, 7 research hot spots were founded.

Conclusion: Our data indicated that NIPT mainly focuses on the 7 major research hot spots, and strategic diagram provides some hints for the future research trend of NIPT.

Introduction

Non-invasive prenatal testing (NIPT) is a new prenatal screening method that analyzes cell-free DNA (cfDNA) in the blood of a pregnant woman for detecting fetal chromosomal aneuploidies. Since its introduction into clinical practice in 2011, NIPT has been rapidly adopted as a screening option for common chromosome aneuploidies, mainly for trisomy13, trisomy18, trisomy 21 and sex chromosome aneuploidies(SCAs) ^[1, 2]. Before the emergence of NIPT, maternal serum screening and ultrasound imaging (ultrasonography) are commonly used to detect chromosome aneuploidies and other birth defects, which are a routine part of prenatal care in the first trimesters ^[3]. Compared with these two detection methods NIPT has the advantage of high sensitivities and low false positive rates. Because NIPT is a maternal blood test, there is no risk of procedure-related pregnancy loss ^[4]. The appearance of NIPT enriches the prenatal testing program and greatly reduces many unnecessary invasive tests, such as villus biopsy, amniocentesis and umbilical cord blood puncture. Since NIPT can effectively reduce the abortion rate, it also reduces the anxiety of pregnant women ^[5]. It brings a great impact on the traditional prenatal examination mode, and has become one of the important technologies in prenatal screening. Although a rapidly growing number of publications, advancements and novel concepts have been published about NIPT in recent years ^[6, 7], few attempts have been made to systematically analyze NIPT.

Bibliometrics is a set of special methods that are conducted for the quantitative analysis and deciphering of hot spots in the literature, and has been used in various fields to assess the productivity [8]. In the present study, we performed bibliometric methods such as co-citation and co-occurrence analysis to explore the history, current status, and future trends in NIPT. Using this approach, we investigated the theme trends and intellectual structure of the publications in the NIPT field. From a bibliometrics perspective, this study provides a scientific basis and clinical guidelines of NIPT use for researchers and clinical doctors.

Materials And Methods

Sample collection

Data were retrieved and downloaded from PubMed (US National Center for Biomedical Information, NIH, MD, USA). PubMed is a free authoritative medical literature database of the National Library of Medicine on the Web, and articles from Medline (a subset of PubMed) are indexed with MeSH (Medical Subject Headings) terms. MeSH is the National Library of Medicine curated medical vocabulary resource that has been applied to reflect the contents of articles. Query is detailed as follows: (non-invasive prenatal testing OR non-invasive prenatal test* OR Noninvasive prenatal testing OR NIPT OR Noninvasive prenatal test*) AND ("2011/01/01"[Date-Publication]: "2020/012/31"[Date - Publication])). Base on the above query, two researchers independently reviewed and evaluated the studies and reached consensus on the inclusion for analysis. Any discrepancies were discussed with reference to the research objective until consensus was reached. Initially, 2160 related articles were identified in this study.

Data extraction & bibliographic matrix construction

We used the bibliographic Item Co-Occurrence Matrix Builder (BICOMB) (developed by Professor Cui from China Medical University and available freely online) [9] to extract data of publication year, country, language, journal name, and major MeSH terms from the retrieved sample set. Microsoft Excel were used to count the frequency of each item. We set a threshold to extract the high-frequency MeSH terms using the Donohue equation:

$$T = (1 + \sqrt{1+8i})/2,$$

where 'i' denotes the number of major MeSH terms to that appears only once [10]. Then, the term-paper matrix and term co-occurrence matrix were constructed by using BICOMB software.

Blustering analysis of the high-frequency major Mesh terms

The clustering analysis of high-frequency major MeSH terms was employed to classify the major MeSH terms based on the term- paper matrix. The repeated bisection algorithm in g-cluto software (<http://glaros.dtc.umn.edu/gkhome/cluto/gcluto>) results in clustering mountain visualization and in constructing a visual matrix ^[11]. For mountain visualization, each peak in the 3D terrain labeled by a number represents the clusters analyzed by clustering. The location, volume, height and color of each peak location on the plane were employed to interpret the information relating to the clusters and their associations. For matrix visualization, the row labels stand for the high-frequency major MeSH terms respectively on the right. The color of each grid represents the relative occurrence frequency of a MeSH term in an article. Rows of the same cluster are aggregated and black horizontal lines separate these clusters ^[12].

Strategic diagram analysis

Strategic diagram was utilized to interpret internal and external cohesion of a specific research field by Law et al. ^[13]. Based on the co-occurrence matrix, we calculated the centrality and density of each theme cluster. We built a 2D strategic diagram by plotting themes along two axes. The x-axis represented centrality or the external cohesion index, namely the central position of the theme. The y-axis represented density or the internal cohesion index, namely the development of the theme. Four quadrants were generated with the X- and Y-axis. Themes located in Quadrant I (upper right), with both strong centrality and high density, were central themes in this field. Themes in Quadrant II (upper left) with inadequate external interactions but high density were defined as peripheral but already well-developed themes. Themes in Quadrant III (lower left) with weak density and inadequate centrality were both peripheral and undeveloped. Quadrant IV (lower right) contained themes with strong centrality but weak internal maturation. The clusters in Quadrant III and IV are becoming mature to some extent ^[14]. The above mentioned 7 hot spots were then allocated into these four quadrants according to the results of the clustering analysis. Furthermore, the Excel software was used to generate a strategic diagram.

Result

Growth of the Literature

Based on the search strategy and inclusion criteria, a total of 2160 publications were included in this study. The year with the largest volume (335 articles) of published literature was 2020. The average number of these publications per year was about 216. As shown in Fig 1, the distribution of the publications during the period of 2011 to 2020 was steady increased.

Distribution of Countries

According to the data, at least 32 different countries or regions were indexed. According to the number of articles published in journals, we list the top ten journals (Fig 2). The 542(25.1%) articles were published from United States who ranked first place and 10.5% higher than China whose publications number was 316(14.6%) ranking the second place.

Most active Journals

Fig 3 listed the top 10 journals whose inclusion criteria was the number of published articles should be more than 20 on NIPT from 2011 to 2020. The 10 most active journals published 633 of all 2160 publications (29.3%). The Prenatal diagnosis ranked first with 261 publications (12.1%), which indicated this journal may be better keeping abreast of research progress about NIPT.

Research Hot Spots of Non-invasive prenatal testing

A major MeSH term with a frequency of 21 or more than 21 times occurrence was defined as a highly frequent term. As shown in Table 1, 37 highly frequent major MeSH terms were extracted from the included publications with a cumulative percentage of 64.8%. These MeSH words were submitted for clustering analysis with the different numbers of clusters. The clustering result of the matrix of highly frequent major MeSH was used to plot mountain visualization and matrix visualization. After clustering analysis, these MeSH terms were classified into five clusters, and mountain visualization with the highly frequent MeSH terms in each cluster was generated—show in Fig 4. Each cluster was represented as a peak in the three-dimensional terrain labeled by the cluster number (0 through 4). The height of each peak was proportional to the cluster’s internal similarity. In Fig 4, each cluster showed an independent and high peaks which indicated the cluster’s internal similarity was good. The color of a peak represented the internal standard deviation of a cluster’s objects, where red represented a low deviation whereas blue represented a high deviation. Cluster 0 and Cluster 1 showed red color which means better internal standard concentricity. Cluster 1 shows the best of all clusters. The researches content of this part accounted for the largest proportion.

Table 1

Highly frequent major MeSH terms from the included publications on NIPT

Rank	Highly MeSH terms	n	p%	Cp%
1	Prenatal Diagnosis	823	15.4	15.4
2	Genetic Testing	314	5.9	21.3
3	DNA	262	4.9	26.2
4	Down Syndrome	234	4.4	30.6
5	Chromosome Disorders	181	3.4	34.0
6	Aneuploidy	174	3.3	37.3
7	Maternal Serum Screening Tests	161	3.0	40.3
8	Trisomy	128	2.4	42.7
9	Cell-Free Nucleic Acids	126	2.4	45.0
10	Fetus	92	1.7	46.8
11	Noninvasive Prenatal Testing	74	1.4	48.2
12	Fetal Diseases	72	1.3	49.5
13	High-ThroughputNucleotide Sequencing	70	1.3	50.8
14	Sequence Analysis, DNA	68	1.3	52.1
15	Chromosome Aberrations	63	1.2	53.3
16	Ultrasonography, Prenatal	58	1.1	54.4
17	Genetic Counseling	43	0.8	55.2
18	Genetic Diseases, Inborn	38	0.7	55.9
19	Sex Determination Analysis	32	0.6	56.5
20	Pregnancy Trimester, First	32	0.6	57.1
21	DNA Copy Number Variations	30	0.6	57.6
22	Amniocentesis	28	0.5	58.2
23	Pregnancy	26	0.5	58.7
24	Prenatal Care	26	0.5	59.1
25	Decision Making	26	0.5	59.6
26	Congenital Abnormalities	25	0.5	60.1
27	Mosaicism	25	0.5	60.6
28	Polymorphism, Single Nucleotide	25	0.5	61.0

29	Placenta	24	0.4	61.5
30	Sex Chromosome Aberrations	24	0.4	61.9
31	Chorionic Villi Sampling	23	0.4	62.4
32	Mass Screening	22	0.4	62.8
33	Mothers	22	0.4	63.2
34	Health Knowledge, Attitudes, Practice	22	0.4	63.6
35	Polymerase Chain Reaction	21	0.4	64.0
36	Trisomy 18 Syndrome	21	0.4	64.4
37	Chromosome Deletion	21	0.4	64.8
Frequency of the MeSH terms; n: Frequency of the MeSH terms; p%: percentage of MeSH terms in the total cp%: cumulative percentage of MeSH terms in the total				

The matrix visualization of NIPT

Fig 5 shows the matrix visualization where the row labels denote the major high frequency MeSH terms (on the right). Colors were used to graphically represent the values present in the matrix, where the color of each grid represented the relative occurrence frequency for a MeSH term in an article. The darker shade of the red color represented larger values and the white color represents the values near zero. The rows in the primary matrix were reordered by clustering, where rows of the same cluster were aggregated and black horizontal lines separated the clusters (Fig 5). The matrix visualization revealed that 37 major highly frequent MeSH terms were clustered into 5 clusters. The right hierarchical tree depicted the relationships between highly frequent major MeSH terms. The remaining hierarchical tree depicted the relationships between the major high frequency MeSH terms. Representative articles in each cluster were employed to identify and summarize the themes for each cluster. According to these MeSH words, We summarize 7 topics from the 5 clusters: 1) NIPT, a new screening method of prenatal diagnosis (Cluster 0); 2) Karyotype analysis of amniocentesis remains the gold standard for prenatal diagnosis of fetal chromosomal abnormalities which can not be replaced by NIPT (Cluster 0); 3) NITP is based on high-throughput sequencing and statistical calculation analysis (Cluster 1); 4) Genetic counseling and interpretation (Cluster 2); 5) NIPT for monogenic diseases (Cluster 3) 6) Evaluation of NIPT in fetal sex determination (Cluster 3); 7) Evaluation of NIPT in detecting sex chromosome abnormality (Cluster 4).

Strategy diagram for NIPT

In this study, the strategic diagram represented the knowledge structure of NIPT in the last 10 years from 2011 to 2020, and clusters were presented by spheres organized in different quadrants according to their calculated density and centrality, which represent their internal and external cohesion, respectively (Fig .6). The cluster 4 in quadrant I were central themes in the general network. The density of clusters 1 was the best among all clusters, suggesting that detection of cffDNA by high-throughput nucleotide sequencing and clinical application of NIPT related research has formed a certain degree of maturity. The clusters 0 and 2 were in quadrant III, which means treated NIPT as a clinical diagnostic test and genetic counseling and interpretation of NIPT have not been fully developed, suggesting that these themes should be improved in the future. The cluster 1 and 3 was in quadrant IV, suggesting that NIPT used to diagnose monogenic disease are still at the initial stage. The strategic diagram indicated the tendency and development of each theme cluster of NIPT from 2011 to 2020.

Discussion

The number of studies on prenatal gene screening has soared with increasing awareness of its potential clinical test applications. NIPT have become an emerging research field, which requires the systematic analysis of its trends and knowledge structure. With that in mind, the present study revealed an increase in publications and 7 hot spots of research on NIPT from a quantitative and qualitative analysis of view. As expected, the number of publications was less before 2011 and started to steady increased during the period of 2011-2020. The maximal number of publications was found in 2020. Currently, the United States is still the top country for NIPT publications. In terms of all countries for NIPT publications, the major contributions were from a small number of developed countries in North America, Europe, and China. This may be due to the fact that gene sequencing technology has been developed earlier in these countries and regions.

In this study, we found that the 10 most active journals published NIPT related publications (accounting for 29.30% of all 2160 publications), and thus were considered as the core journals in the NIPT field. The Prenatal Diagnosis ranked the top among the 10 active journals. Methodologically, the present study used the clustering analysis and visualization method to identify hot topics on inputting the g-cluto software. Altogether, 7 research hot spots of NIPT were found, as follows:

1) NIPT, a new screening method of prenatal diagnosis (Cluster 0).

With the rapid development of high-throughput sequencing technology and Professor Dennis Lo's team found that there is fetal dissociation in the peripheral blood of pregnant women. NIPT has been widely used in prenatal congenital malformation screening because of its high sensitivity and low false positive rate. Before NIPT came into clinical application, pregnant Down's syndrome screening played an

important role in the pregnancy examination of trisomy 21, trisomy 18 and trisomy 13. Although the detection rate of 21- trisomy, 18- trisomy and 13- trisomy can be increased to 80%-94%, the false positive rate was very high (about 5%), which causes a lot of unnecessary anxiety for pregnant women. NIPT provides additional choices for prenatal testing which has already replaced the serological screening but can not replaced the amniocentesis karyotype analysis. The reasons will be analyzed in detail in the next paragraph.

2) Karyotype analysis of amniocentesis remains the gold standard for prenatal diagnosis of fetal chromosomal abnormalities which can not be replaced by NIPT (Cluster 0)

Various of factors will affect the accuracy of the NIPT results, for example, (1) lower concentration of cffDNA. cffDNA was existed in maternal peripheral blood, the percentage of which is generally at the range of 3%-30%, with the average of 13%. Most current NIPT protocols utilize 4% as the lower percentage cutoff value to ensure a reliable result ^[16]; (2) the chromosome abnormalities of mother. Liu J et al. have reported a confirmatory amniocentesis and karyotyping test taken from 563 patients who have received a positive trisomy result by NIPT. and revealed 489 true and 74 false positives. In 6 of these 74 patients (8.1%), CNV-Seq were performed to these 74 patients, 6 of which revealed non-pathogenic maternal duplications (1.76–10.90 Mb) on the chromosome associated with the fetal trisomy. Maternal CNVs may cause false-positive NIPT trisomy results, and there was a strong correlation of higher Z-scores with increasing size of maternal CNVs ^[17]; (3) The Confined placental mosaicism (CPM). Mosaicism in general is a biological phenomenon when two or more chromosomally distinct cell lines arising from a single zygote are both found in an individual. As we know, cffDNA was derived from embryonic trophoblast cells rather than fetal sources, so CPM was one important cause of false positive results in NIPT. No matter what the reason caused NIPT results are positive, all should be verified by confirmed experiments. As NIPT can be performed starting at 10 weeks gestation, asking a couple to wait until after 16 weeks for an amniocentesis to be performed can represent an unacceptably long and stressful waiting time for parents. An earlier option for further testing would be with chorionic villus sampling (CVS), which can be performed at a much earlier gestational age than amniocentesis (11–13 weeks) ^[18]. No matter which test is chosen, further confirmation experiments are necessary.

3) NITP is based on high-throughput sequencing and statistical calculation analysis (Cluster 1)

Different from ultrasound and serum biochemical screening, NITP is based on high-throughput sequencing and statistical calculation analysis ^[19]. NIPT has been used to screen for the common fetal aneuploidies, trisomy 13, 18, 21 and expended to detect rare autosomal aneuploidies (RATs) and CNVs in

recent years. For example, a retrospective analysis was performed on total 24,702 pregnant women who took the expanded NIPT. The sensitivity of expanded NIPT was 100% (95% confidence interval [CI], 97.38-100%), 96.67% (95% CI, 82.78-99.92%), and 100% (95% CI, 66.37-100.00%), and the specificity was 99.92% (95% CI, 99.87-99.96%), 99.96% (95% CI, 99.91-99.98%), and 99.88% (95% CI, 99.82-99.93%) for the detection of trisomies 21, 18, and 13, respectively. Expanded NIPT detected 45, X, 47, XXX, 47, XXY, XYY syndrome, RATs, and CNVs with positive predictive values of 25.49%, 75%, 94.12%, 76.19%, 6.45%, and 50%, respectively ^[20]. The study demonstrated that the expanded NIPT detects fetal trisomies 21, 18, and 13 with high sensitivity and specificity. However, the accuracy of detecting SCAs, RATs, and CNVs is still relatively poor and needs to be improved.

(4) Genetic counseling and interpretation (Cluster 2)

As NIPT is widely used in detecting chromosomal aneuploidies, informed decision-making has become the major ethical concerns. Before agreeing to screening tests, parents need to be fully informed about the risks, benefits and possible consequences of such a test. This includes subsequent choices for further tests they may face, and the implications of both false positive and false negative screening tests. The decisions that may be faced by expectant parents inevitably engender a high level of anxiety at all stages of the screening process, and the outcomes of screening can be associated with considerable physical and psychological morbidity ^[21]. A study investigated that the impact of genetic counselling has indicated that many women do not make informed decisions about prenatal genetic screening, and the introduction of genomic technologies has generally added to the ethical debate ^[22]. Appropriate pre- and post-test genetic counselling is recommended, and healthcare providers should include balanced information, as well as psychosocial support so that couples can get comprehensive understanding and make right decisions. Comprehensive pretest and posttest counseling is recommended and should address the importance of confirmatory testing and benefits of early diagnosis. Practice guidelines are needed to address provider responsibilities about postnatal testing.

(5) NIPT for monogenic diseases (Cluster 3)

NIPT has been widely adopted for the detection of fetal aneuploidies and CNVs in the past year. This paragraph will focus on the application of NIPT in the diagnosis of monogenic diseases. Initially, NIPT of monogenic disorders focused on detecting de novo or paternally inherited variants responsible for dominant monogenic disorders ^[23]. Overall, the approaches of NIPT in recessive diseases are typically classified into two categories: relative mutation dosage (RMD) analysis ^[24] and relative haplotype dosage (RHDO) analysis ^[25]. The principle of RMD was quantitative comparisons between variant and wild-type alleles present in cfDNA. RMD was mainly detecting single nucleotide variants (SNVs) and small insertions/deletions (InDels) but cannot detect large InDels and CNVs; RHDO approach determines the relative proportions of variant and normal haplotypes in maternal plasma ^[26] and can theoretically detect most types of variants, including large InDels and CNVs ^[27]. However, RHDO analysis requires parental

haplotype information and the detection cost was very expensive. The latest research reported a novel approach to detecting Thalassemia, which is based on population-based haplotyping-NIPT (PBH-NIPT) [28]. The PBN-NIPT provide a simple, fast, and inexpensive method. Compared with the traditional linked-read sequencing based NIPT method, the PBN-NIPT only cost 5-7 day to finish lab work and data analysis. Meanwhile, the detection cost is reduced from 1500 dollars/sample to 80 dollars/sample.

(6) Evaluation of NIPT in fetal sex determination

NIPT is a rapidly adopted prenatal testing method, which uses cell-free DNA to detect a range of genetic and chromosomal diseases, and determine fetal sex earlier, more easily and more reliably. Therefore, NIPT potentially expands the market for sex determination and sex selective abortion. For example, Ho et al. reported that fetal sex was correctly determined in 77 of 82 (93.9%) cell-free DNA samples of pregnant women of 6-39 gestational weeks, and confirmed that fetal sex was determined as early as 6 gestational weeks using cell-free DNA from maternal plasma [29]. Another study by Koumbaris and Kypri has developed an assay for the detection of fetal aneuploidies of sex chromosomes based on the targeted analysis of cell-free DNA, which can correctly identify fetal sex in all cases (95% CI, 99.4%-100%) [30]. Both studies indicate that cell-free DNA analysis exhibits high accuracy in fetal sex determination.

(7) Evaluation of NIPT in detecting sex chromosome abnormality (SCAs)

SCAs is estimated to be one in every 500 live births, between 75% and 90% of cases remain undiagnosed in their lifetime. Children with these disorders may present with dysfunction in speech, language, and motor development. A retrospective population-based cohort study from 1986–2016 of pregnant women undergoing NIPT has provides a very meaningful set of data. With the emergence and application of NIPT detection technology, the percentage of prenatal diagnostic tests leading to a SCAs diagnosis increased significantly from 0.95% in 2010 to 2.93% in 2016 [31]. This data showed that NIPT can effectively reduce the occurrence of fetal sex chromosome abnormality. However, NIPT also has limitations in detecting SCAs. For example, a study screening for SCAs in 9985 pregnancies by NIPT has showed the false positive rate of SCAs was 22.5%. Expecially in this case of 45, X0, the false positive rate is as high as 47% [32]. Therefore, screening for s SCAs by NIPT is still controversial.

Limitation and Expectation

Although NIPT based on cell-free DNA in maternal circulation has been accepted worldwide by the clinical community, several limitations such as maternal malignancy and fetoplacental mosaicism, maternal mosaicism, and a demised co-twin, preclude its full replacement of invasive prenatal diagnosis [33]. Many attentions have focused on both fetal nucleated red blood cells and trophoblasts [34]. A novel silicon-

based nanostructured microfluidics platform has been reported to be feasible to capture circulating fetal nucleated red blood cells and extra villous cytotrophoblasts for cell-based noninvasive prenatal diagnosis^[33]. We have enough confidence that NIPT will replace maternal serum screening (MSS) and invasive testing in the future. By that time, lacking of physician education on NIPT may become the major barriers for its implementation. Data from health care providers (HCPs) have indicated that counseling a patient after a failed cfDNA NIPT is challenging, reinforcing that this can possibility be covered by pre-test a counseling^[35]. Along with the perfection of detecting techniques and the complete genetic counseling system, NIPT will provide more benefits for prenatal diagnosis.

Conclusions

In this study, content analysis by co-word biclustering was employed to visualize research hot spots in the field of NIPT. Based on our search strategy, a total of 2160 publications were included in this study. The United States is the country with the most extensive application and the maximum number of published articles of NIPT. 7 research hot spots were summarized from this article to expound the advantages and disadvantages of NIPT, which may provide some hints for the clinical application and further improvement.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ting Fan retrieved and downloaded from PubMed and used the bibliographic Item Co-Occurrence Matrix Builder (BICOMB) to extract data of publication year, country, language, journal name, and major MeSH terms from the retrieved sample set. Bijun zhang was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

No conflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication.

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Figures

Figure 1

Number of the published articles from the year 2011 to 2020. The distribution of publications on NIPT in PubMed for each year and the number of publications on NIPT in PubMed accumulated year by year.

Figure 2

The country distribution of NIPT publications in PubMed from 2011 to 2020.

Figure 3

The journal distribution of NIPT publications in PubMed from 2011 to 2020.

Figure 4

Mountain visualization of biclustering of highly frequent major MeSH terms on NIPT.

Figure 5

Visualized matrix of biclustering of highly frequent major MeSH terms on NIPT.

Figure 6

Strategic diagrams for NIPT.