Discover Oncology

Review

A bibliometric analysis of nucleic acid probe and its applications in oncology: towards more precise molecular medicine

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Received: 6 November 2024 / Accepted: 23 April 2025
Published online: 08 May 2025

Abstract

Background Nucleic acid probes, which are short sequences of nucleic acids designed to complement specific DNA or RNA targets, have broad applications in biosensing, genetic studies, and various other fields. In tumor diagnosis and treatment, nucleic acid probes offer a precise and accessible approach that is essential for improving patient care and quality of life. Despite substantial research on nucleic acid probes over the past three decades, few comprehensive reviews have retrospectively examined the field.

Methods This study extracted 30 years of nucleic acid probe-related research articles from the Web of Science Core Collection database. We used CiteSpace, VOSviewer, and R tools to systematically analyze the field's current status and developmental trends, with an emphasis on applications in oncology.

Results Our findings indicate a continuous growth trend in nucleic acid probe research, with the United States and China, along with their leading institutions and authors, making the most significant contributions. In oncology specifically, nucleic acid probe research has focused primarily on signal amplification, liquid biopsy, and drug delivery. The emergence of novel biomarkers and assay techniques has been a pivotal factor driving advancements in this field.

Conclusion Nucleic acid probes show strong potential for applications in tumor precise diagnosis and treatment. Continued innovation and closer interdisciplinary collaboration will be vital for further advancements, while large-scale clinical studies are needed to validate their clinical utility.

Keywords Nucleic acid probe · Oncology · Bibliometric analysis · Biosensor · DNA · RNA

1 Introduction

Nucleic acids, as the most fundamental substances of life, are characterized by programmable base sequences, unique molecular recognition, stimulus-triggered reactivity, and convenient synthesis and modification [1–4]. With the rapid development of research and innovation in molecular biology, multifunctional molecular probes using nucleic acids as the basic framework, termed nucleic acid probes (NAPs), have become indispensable tools for the accurate detection

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-02478-3.

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and analysis of nucleotide sequences, the applications of which span across biosensing, bioimaging, and medical diagnostics [5–8]. As the use of NAPs expands in various fields, scientific research is converging. One significant advantage of NAPs, compared to traditional detection methods, is their inherent specificity, enabling precise mapping of nucleotide sequences [9–11]. Fluorescent hybridisation probes can distinguish between two DNA sequences that differ by only one nucleotide, an advantage that not only promotes experimental versatility but also enables researchers to customize their methods to meet specific research requirements [12–14]. Finally, it is also easy to synthesise, robust and low cost [15–17].

The increasing morbidity and mortality rates associated with cancer pose a major challenge to global health, as well as an enormous economic and medical burden on individuals, families and communities [18–21]. Therefore, early diagnosis of cancer is particularly important. The most commonly used diagnostic method is cancer biomarker detection in serum (e.g., enzyme-linked immunosorbent assay, ELISA) [22–24]. However, complex serum and plasma components make it difficult to detect low concentrations of cancer biomarkers, which hampers early diagnosis of cancer [25–27]. These necessitate a shift towards more precise and targeted approaches as well as effective early detection strategies. Technological advances in the study of circulating biomarkers from the patient's blood have made this strategy possible. Liquid biopsy markers including circulating tumour cells (CTCs), extracellular vesicles (EVs), circulating tumour DNA (ctDNA) and exosomes are considered to be a more practical method of real-time patient monitoring than conventional tumour biopsies [28–30]. Liquid biopsy is a minimally invasive method of obtaining information about the source of a tumour from body fluids (usually blood). Circulating DNA (cell free DNA, cfDNA) is released into the bloodstream from living cells via extracellular vesicles or during cell death. In the physiological state, cfDNA levels range from 1.7 to 100 ng/mL in blood [31] and 12–439 ng/mL in urine [32]. In cancer patients, the concentration of cfDNA in the blood can be substantially elevated, ranging from 50 to 1000 ng/mL, with tumour DNA accounting for 3–90% of the total cfDNA pool [33–36]. cfDNA has become a promising research area for diagnostic, prognostic and efficacy testing [37–39], so that NAPs have made significant contributions to targeted therapies and personalized medicine models in cancer treatment by interacting with cfDNA [40–42]. They offer the significant advantage of non-invasively monitoring disease-related genetic alterations in body fluids [43–45]. Moreover, their non-invasiveness and ability to enhance patient compliance with routine screening programs make them highly valuable. Clinicians can utilize these probes to detect minute genetic alterations indicative of cancer in body fluids, offering a minimally invasive yet highly sensitive method for early cancer detection [46–48]. This not only minimizes patient discomfort but also presents an attractive avenue for routine screening, with the potential to revolutionize early cancer detection [49–51]. They can specifically target and bind to cancer-associated gene sequences, leading to the development of targeted therapies that minimise collateral damage to healthy cells and improve efficacy [52–54].

Imaging analysis using NAPs can more accurately detect and identify genetic mutations in cancer cells, such as EGFR mutations in non-small cell lung cancers, as well as mutations in circulating tumor DNA or other sample with low tumor content and low mutant allele burden, to better guide the utility of targeted agents and predict patients prognosis outcomes [55–59]. For example, the FISH test is an important testing technique widely used in the medical field. The full name of FISH is fluorescence in situ hybridisation. The technique is able to accurately detect and locate specific sites on chromosomes, genes, or sequences through the use of fluorescently labelled DNA or RNA probes [60–62]. FISH examination can provide accurate and high-resolution molecular information that can help determine the presence or absence of some genetic abnormalities, mutations or chromosomal rearrangements. In clinical practice, FISH examination can be applied to detect tumour-associated genetic variants, providing an important auxiliary basis for the diagnosis, staging and treatment of tumours [63–65].

In addition, nucleic acid fluorescent probes may open new avenues for precision treatment by converting biometric events into amplified signals, particularly through intracellular markers and/or fluorescence sensing and imaging, to guide surgical procedures [66–68]. These probes hold the potential to improve efficacy and reduce side effects, deviating from the traditional "one-size-fits-all" treatment paradigm [69–71].

Bibliometrics is a discipline that investigates the quantity, quality, citation relationships, and impact of scholarly literature [72–74]. It provides a global repository of literature for academics and promotes academic exchange and cooperation between disciplines and countries. Through bibliometrics, researchers can identify international cutting-edge papers and research teams relevant to their own research, expanding academic networks and bringing new opportunities for collaboration. By quantitatively analyzing literature data, bibliometrics reveals trends in academic research, the contributions of researchers, and the direction of disciplinary development. It reveals new knowledge and discovers potential connections and breakthroughs in the discipline through mining and analysing a large amount of literature data. Through bibliometrics, researchers can mine and discover innovative and forward-looking research directions, thus promoting the further development and innovation of the discipline. Utilizing bibliometrics

allows researchers to gain a comprehensive understanding of research dynamics in the medical field, thereby providing robust support for research decisions and academic communication [75–77].

As the first bibliometric study in the field of NAPs, this article aims to comprehensively analyze the current status and trends of the development of the NAP. Special emphasis is placed here on its development in Oncology, displaying its significant value in precision medicine so as to facilitate more accurate tumor diagnosis and therapy.

2 Materials and method

2.1 Data source and search strategy

Web of science is chosen as a source for literature search, and this informative global citation database often serves as the first choice for researchers (Fig. 1). Further, we chose the Web of Science Core Collection database as a data source to improve its representativeness and reliability. The main keywords "nucleic acid probe" and "Neoplasms" were used to conduct the subject search covering the period from 1994.01.01 to 2024.11.01 (Table S1). Subsequently, complete records and cited references were extracted from relevant publications and saved in plain text format.

2.2 Analytical method

In this study, three tools, CiteSpace 6.2.R4 [78], VOSviewer 1.6.20 [79], and R version 4.2.2 [80], were used for bibliometric analysis and visualization. Bibliometrix R package version 4 [81] was used to calculate the number of citations in the literature as well as the collaborations between countries. Collaborations between countries, institutions and authors were analyzed by VOSviewer software. CiteSpace was used to perform co-occurrence network, cluster analysis and emergence analysis of disciplines, keywords and cited publications. Here, the time frame was 1994 to 2024 with a time slice of 1 year. Keywords were filtered with a threshold of frequency greater than 20, and the top 100 were selected as nodes for visualization.

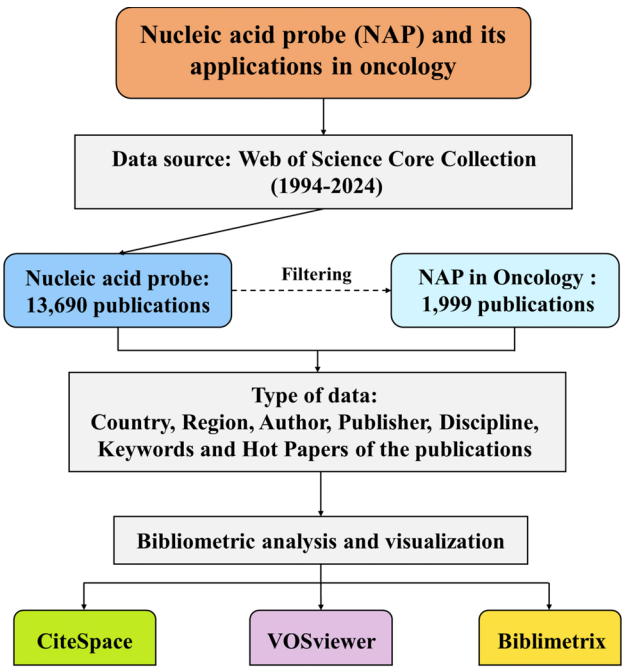

Fig. 1 Flow-chart of the study

3 Results

3.1 Nucleic acid probes

3.1.1 Quantitative analysis of basic information

The field of NAPs comprises 13,680 articles. Considering the establishment of WOS in 1997, pre-1996 publications are sparsely indexed, with fewer than 10 documents retrievable from that period. Since 1997, the number of articles has gradually increased steadily and slowly, and there have been 634 articles by 2024 (Fig. 2a). Therefore, we believe that this field is an active research area and has received a lot of attention from scholars.

The United States and China are the most influential countries in the field, with 9194 and 8516 studies, respectively, surpassing other countries such as Germany, Japan, France, the United Kingdom, Canada, and Italy (Fig. 2b). Analyzing the collaborative efforts between these countries/regions, the closest collaborations were observed between China and the United States (259 studies), followed by the United States and Germany (105 studies), the United States and the United Kingdom (88 studies), and the United States and Canada (78 studies). Figure 2c visually represents the number of publications per country. These findings highlight the prominent global leadership of the United States in the field of NAPs. VOSviewer visualization analysis (Fig. S1) further substantiates the central role of the United States, while other countries are divided into six main clusters, geographically dispersed around the United States. Notably, countries within the same cluster exhibit closer cooperation in this field. Figure S2 provides additional visual representation of intercountry cooperation.

A total of 1927 institutions worldwide have published relevant papers. Among the top 20 institutions in terms of the number of published papers (Fig. S3), 12 are from the United States, 4 from France, 2 from China, 1 from Canada, and 1 from Russia. The predominance of US institutions further emphasizes their dominant position in the field. The Chinese Academy of Sciences leads with 900 papers, followed by Centre National De La Recherche Scientifique (CNRS) with 519 papers, University of California System with 359 papers, and State University System of Florida with 346 papers. Hunan University, University of Florida, and University of California System also contribute significantly with 286, 202, and 198 articles, respectively. Notably, China and France emerge as major contributors. Collaboration analysis and visualization indicate that 41 institutions have published at least 57 papers, forming six clusters characterized by close inter-institutional cooperation (Fig. S4). The first cluster, represented in red, primarily consists of American institutions such as Stanford University and Johns Hopkins University. The second cluster, shown in blue, includes Chinese institutions like Hunan University and Xiamen University, as well as the University of Florida and the Russian Academy of Sciences. The third cluster, depicted in yellow, comprises Chinese institutions such as Tsinghua University and Sichuan University. The fourth cluster, shown in green, involves institutions like Nanjing University, Shandong University, and the National University of Singapore. Finally, the fifth cluster, denoted by purple, encompasses the Chinese Academy of Sciences and Cornell University.

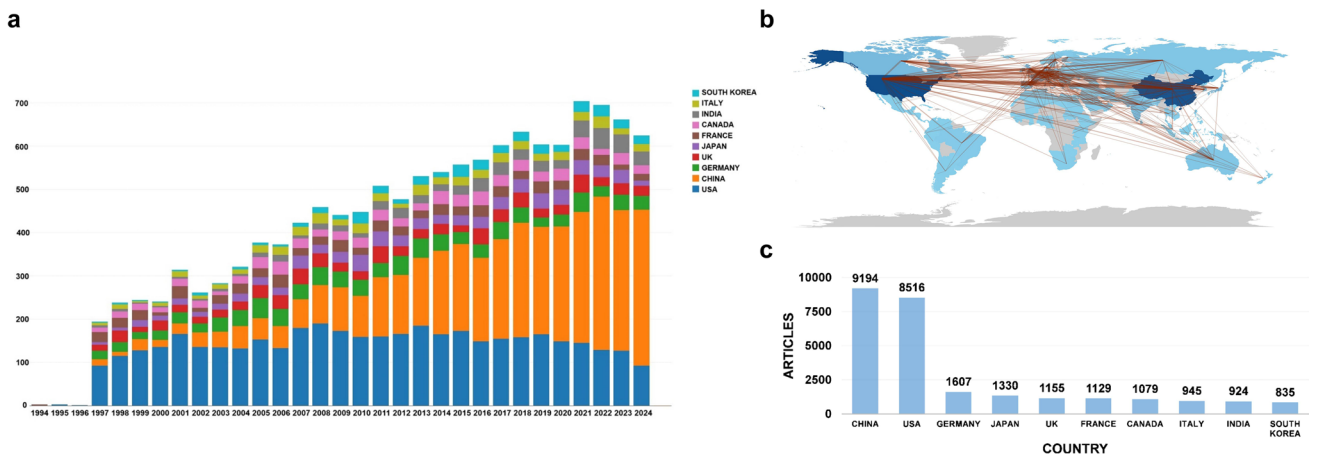

Fig. 2 Characterization of research distribution in the field of NAP. **a** Number of publications per year and the cumulative number. **b** Each country's contribution to NAP. **c** Visualizing the number of articles per country, with darker countries having a higher number of articles. **d** The top 20 institutions with the most publications in the field of NAP

Table 1 Top 10 journals in the field of NAP

No	Sources	Articles	CiteScore	IF(2023)	H-index
1	Analytical Chemistry	569	12.3	6.7	305
2	Biosensors & Bioelectronics	520	20.6	10.7	170
3	Nucleic Acids Research	333	32.3	16.6	452
4	Analyst	252	8.3	3.6	137
5	Journal of the American Chemical Society	251	25.7	14.4	542
6	Analytica Chimica Acta	250	10.7	5.7	180
7	Sensors and Actuators B-Chemical	212	14.6	8.0	170
8	Journal of Clinical Microbiology	185	14.3	6.1	234
9	Talanta	184	12.2	5.6	146
10	Chemical Communications	168	9.9	4.3	297

Table 2 Top 10 authors in the field of NAP

Rank	Authors	Articles	Articles fractionalized
1	WANG L	107	20.23
2	WANG J	105	22.34
3	WANG Y	98	15.79
4	TAN WH	90	14.62
5	LI Y	87	13.08
6	ZHANG Y	82	12.66
7	LI J	77	11.09
8	LIU Y	75	12.79
9	SEITZ O	69	23.41
10	WANG KM	64	8.99

In the field of NAPs, a total of 2116 journals have published relevant articles or reviews. The journals were classified into three categories based on co-citation analysis, represented by Analytical Chemistry, Nucleic Acids Research, and Journal of the American Chemical Society, respectively (Fig. S5). These three journals have high publication output in the field of NAP research and cover distinct areas, including the development of analytical methods and detection technologies, molecular biology and functional exploration, as well as molecular design, chemical synthesis, and the development of innovative materials. This suggests that NAP research is an interdisciplinary field (Table 1).

Table 2 presents the most relevant authors in the field of NAPs. Wang L is the most prolific author with a total of 107 articles and 20.23 fractionalized articles. Wang J has the highest fractionalized articles at 22.34. Co-authorship analysis and co-citation analysis of cited authors were conducted using VOSviewer. The author's co-authorship analysis network (Fig. S6) appears more decentralized compared to the tightly knit network of national and institutional collaborations. Tan Weihong emerges as the author with the highest number of collaborations. Additionally, the time-overlapping authorship analysis network reveals Tan Weihong's early collaboration compared to other authors. Co-citation analysis of cited authors (Fig. S7) categorizes authors into four main segments, with Wang J, Wang Y, Wang L, Tyagi S, and Nielsen Pe serving as central authors. These authors have made significant contributions to the field and are considered crucial figures. Notably, three of them have top 10 articles in the field.

3.1.2 Analysis of discipline evolution

NAPs, consisting of nucleic acid sequences and their molecular hybridization, are closely intertwined with biological and chemical research. Disciplinary co-occurrence analyses in this field can enhance our understanding of the underlying scientific foundations and track trends in NAPs from essential technological perspectives.

Unsurprisingly, chemistry plays a central role in the advancement of NAPs, encompassing several subcategories (Fig. 3a). Notably, chemical analysis stands out as a crucial category since NAPs are application-oriented technologies primarily focused on analytical detection. Electrochemistry also plays a significant role as signal conversion in NAPs often

necessitates electrochemical involvement. Furthermore, NAPs find extensive use in biology as a biochemical research method, falling under the category of "biosensing" and requiring knowledge of biochemistry and molecular biology. NAPs possess structural characteristics of biomaterials with dimensions in the nanoscale. The development of nanotechnology and the study of NAPs are mutually reinforcing, with NAPs serving as an integral component of nanotechnology and, conversely, broadening the scope of NAPs' applications.

The field of NAPs has witnessed an explosion of disciplines involved. As shown in Fig. 3b, disciplinary bursts occurred consistently over the last 30 years, with duration ranging from 2 to 13 years. Among the various disciplines, 'BIOCHEMISTRY & MOLECULAR BIOLOGY' and 'MICROBIOLOGY' have the higher burst strength with earlier emergence. In more recent years, "INSTRUMENTS & INSTRUMENTATION", "CHEMISTRY, APPLIED", "ENGINEERING, ENVIRONMENTAL" and "ENGINEERING, CHEMICAL" have become active new disciplines.

3.1.3 Analysis of hot spots

Keyword analyses provide valuable insights into the most relevant research topics, preferences, and current forefront issues. By examining the keywords in an article, researchers can identify research hotspots and areas of focus.

In this study, a keyword co-occurrence network analysis was conducted, screening 485 keywords with the top 10% frequency of occurrence per year (Fig. 4a). Each node in the network represents a keyword, with its size reflecting the frequency of occurrence. The connections between keywords are represented by connecting lines. The top keywords primarily describe the NAP itself, such as "nucleic acid(s)," "DNA," "probe(s)," and others. Additionally, terms like "hybridization," "resonance energy transfer," and "fluorescence" represent the main research principles of NAPs. On the other hand, "(signal) amplification," "biosensor," "recognition," and "assay" reflect the application process. The intricate interconnections between keywords suggest that they are often studied or discussed in relation to one another.

To gain a more intuitive understanding of the highlighted themes in the field, a cluster analysis of the keywords was performed (Fig. 4b). Keywords that were strongly connected were classified into categories, resulting in six explicit themes denoted by different colors. The first five themes form a closely related "pentagram" structure, which includes "polymerase chain reaction," "nucleic acids," "signal amplification," "oligonucleotides," and "DNA hybridization." Polymerase chain reaction (PCR), as a classical nucleic acid amplification technique, is clustered here to indicate its important role in the application of NAPs. Notably, the application of NAPs can be observed throughout the pre-PCR, PCR, and post-PCR processes. It is interesting to note that "human immunodeficiency virus" emerges as a relatively independent topic, suggesting that it receives frequent attention as a target for NAP testing.

Figure 4c depicts a time-overlapping visualization of the keywords. The node color becomes redder as the time period approaches, and bluer as it recedes. The visualization reveals that in recent years, the research focus has shifted from "hybridization" and "recognition" to keywords like "nanoparticle," "aptamer," "tumor," and others.

Keyword burst analysis can provide insights into frontier research topics. Changes in research hotspots in the field of NAPs occur gradually (Fig. 4d). Initially, the focus was on PCR, sequence, in situ hybridization, and identification. However, recent trends encompass "microRNA", "isothermal amplification", "biomarkers" and more. These findings indicate that applied research in NAPs continuously pushes the boundaries of detection targets and methods.

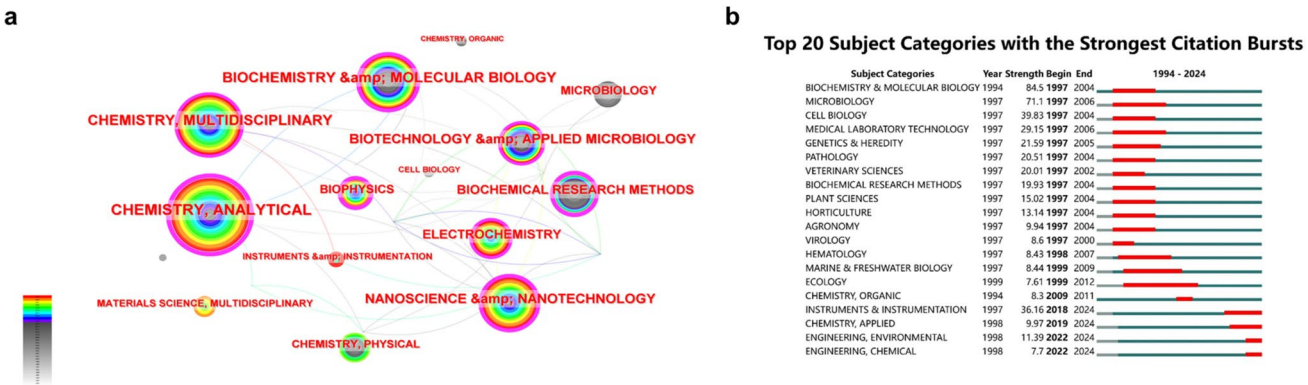

Fig. 3 Disciplinary characteristics of NAP. **a** Disciplinary network analysis in the history of NAP research. **b** The top 20 subject categories with the strongest citation bursts

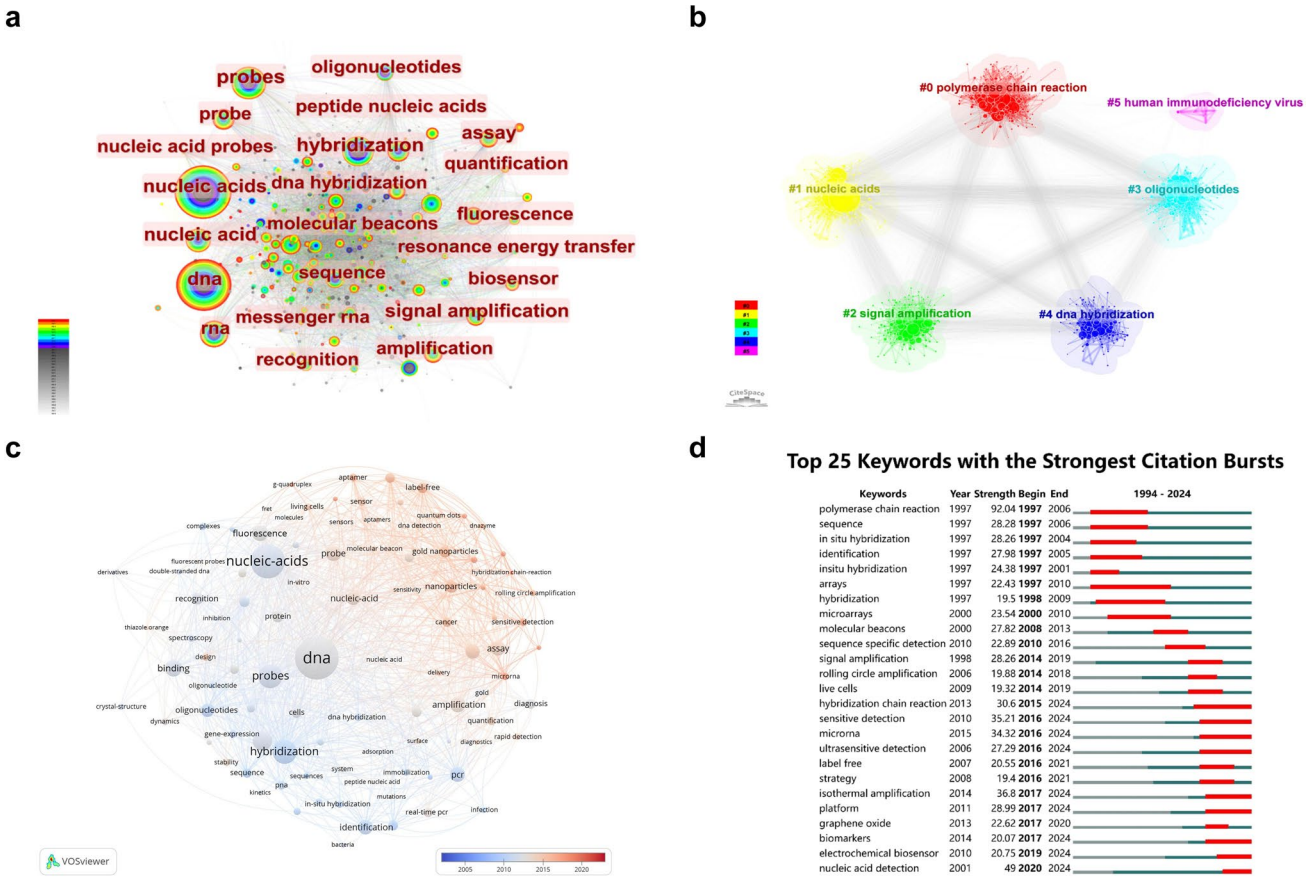

Fig. 4 Keyword analysis in the field of NAP. **a** Keyword co-occurrence network analysis in the field of NAPs. **b** Cluster analysis of keyword co-occurrence in the field of NAPs. **c** Time-overlapping co-occurrence analysis network of keywords in the field of NAPs. **d** The top 25 keywords with the strongest citation bursts

3.2 NAP in oncology

3.2.1 Quantitative analysis of basic information

A total of 1999 articles in the field of NAPs in oncology were published from 1994 to 2024. The number of articles exhibited a rapid increase over the years, rising from 122 in 2003 to 157 in 2018 (Fig. 5a). However, a bottleneck was encountered in 2018, resulting in a decline in 2019, after which the growth rate slowed. These data indicate that the field experienced a period of rapid growth until 2018 but continued to develop overall, suggesting it is an active research area that has garnered significant attention from scholars.

To identify the key countries with a strong influence in the field of NAPs in oncology and analyze their collaborations, we conducted a statistical analysis of the number of papers published in each country/region (Fig. 5b). Throughout the period of 1994–2024, a total of 67 countries/regions published articles on NAPs in oncology. China and the United States emerged as the leading countries, with 2365 and 1119 articles, respectively. The other top 10 countries/regions include Japan, Canada, Germany, Italy, South Korea, the United Kingdom, India, and Spain. A visualization of the number of articles per country (Fig. 5c) confirms the dominance of China and the United States in the field of NAPs in oncology. Additionally, collaboration analysis revealed that the most frequent collaborations occurred between China and the United States (75), followed by China and Singapore (12), and the United States and Russia (11). A co-authorship analysis using VOSviewer illustrated the collaborative relationships between countries (Figs. S8, S9). Notably, Germany and Norway were pioneers in the field, while China joined the research efforts relatively later despite its high number of publications. Figure S10 provides a closer visualization of the cooperation between countries in the field of NAPs and cancer.

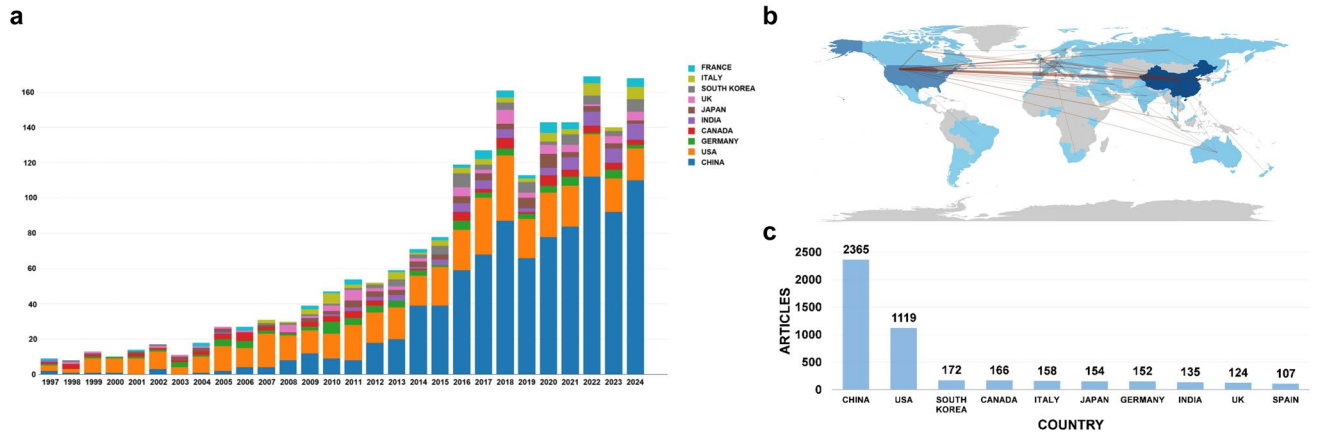

Fig. 5 Characterization of research distribution in the field of NAP in oncology. **a** Number of publications per year and the cumulative number. **b** Visualization of the number of articles per country, with darker countries having a higher number of articles. **c** The top 10 institutions with the most publications in the field of NAP in oncology

We also examined the number of papers published by different institutions worldwide in the field of NAPs in oncology. Approximately 1927 institutions were involved in publishing papers related to this field. Among the top 20 institutions in terms of publication count (Fig. S11), 10 are from China, 6 are from the United States, and 1 each from Singapore, Canada, France, and Thailand. The Chinese Academy of Sciences emerged as the institution with the highest number of publications (166), followed by Hunan University (92), the University of Michigan (59), and the State University of Florida (50). Collaboration analysis and visualization revealed that 121 institutions published at least five papers (Fig. S12). These institutions can be mainly divided into three clusters, all centered around the Chinese Academy of Sciences (CAS) and Hunan University (HU), indicating their significant contributions to NAPs in oncology research. In terms of the time dimension, Peking University and Shanghai Jiao Tong University made important early contributions to the field, while the Chinese Academy of Sciences and Hunan University were more active around 2018.

During the period of 1994–2024, a total of 1723 articles were published in 502 journals. A co-citation visualization (Fig. S13) allowed us to roughly categorize these journals into three segments based on the degree of clustering. The journal "Analytical Chemistry" ranked first with 140 articles, followed by "Biosensors & Bioelectronics" with 113 articles (Table 3). Around 40% of the journals were published by Elsevier. "Nucleic Acids Research," published by Oxford University Press, had the highest impact factor (14.9), citescore (32.3), and h-index (452). The publishers were predominantly from the Netherlands, USA, UK, and Germany.

Table 3 Top 10 journals in the field of NAP in oncology

Rank	Sources	Articles	CiteScore	IF(2023)	H-index
1	Analytical Chemistry	140	12.3	6.7	305
2	Biosensors & Bioelectronics	113	20.6	10.7	170
3	Sensors and Actuators B-Chemical	54	14.6	8..0	170
4	Analyst	50	8.3	3.6	137
5	Analytica Chimica Acta	42	10.7	5.7	180
6	Talanta	40	12.2	5.6	146
7	Nucleic Acids Research	32	32.3	16.6	452
8	Plos One	28	6	2.9	268
9	Analytical and Bioanalytical Chemistry	27	7.5	3.8	149
10	Acs Applied Materials & Interfaces	25	15.7	8.3	169

3.2.2 Analysis of key words

The research hotspots of NAPs in cancer can be identified through keyword co-occurrence analysis. The co-occurrence network diagram (Fig. 6a) reveals a balanced distribution of hotspots in this field. The prominent keywords include "cancer," "DNA," "nucleic acid(s)," and "probes." However, in the context of tumor-related investigations, several new keywords have emerged. For instance, "(gold) nanoparticles" represents the integration of NAPs with nanomaterials, "breast cancer" signifies the most studied tumor type in relation to NAPs, and the use of NAPs in tumor "cells" is also of great interest.

Cluster analysis categorized the findings into six themes (Fig. 6b). While themes #2 ("nucleic acid") and #4 ("hybridization") pertain to the fundamental aspects of NAPs, the other four themes predominantly focus on practical applications such as "signal amplification" during detection, novel sample collection methods like "liquid biopsy," "drug delivery," and "antisense."

The visualization of keyword time-overlapping demonstrates the shifting research focus of NAPs in tumors over the past decade, aligning with the general trend of NAPs (Fig. 6c). Prior to 2018, "gene expression," "PNA," and "hybridization" were the primary research hotspots. In the past five years, the emphasis has shifted towards "nanoparticles," "biosensors," "microRNA," and "signal amplification."

Burst analysis of keywords reveals the latest research hotspots in NAPs for cancer (Fig. 6d). NAPs in cancer research emerged only at the beginning of this century. In the first decade, “gene expression”, “cells”, “polymerase chain reaction” and “in situ hybridization” were the most popular research topics. In recent years, new keywords such as

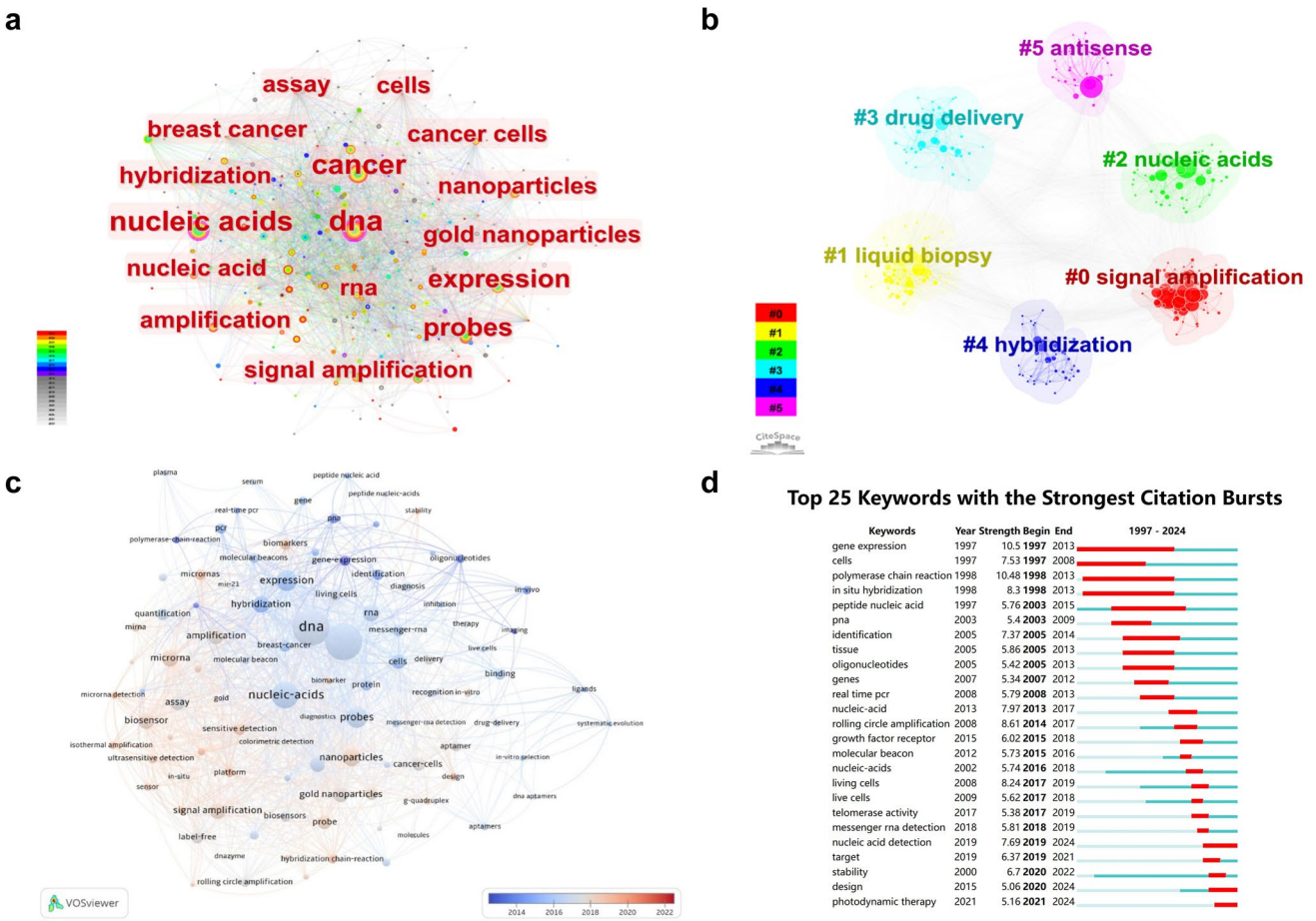

Fig. 6 Hotspot analysis of NAP research in oncology. **a** Keyword co-occurrence network analysis in the field of NAP in oncology. **b** Cluster analysis of keyword co-occurrence in the field of NAP in oncology. **c** Time-overlapping co-occurrence analysis network of keywords in the field of NAP in oncology. **d** The top 25 keywords with the strongest citation bursts. The "Year" denotes the initial emergence of a keyword within the dataset, with "begin" and "end" marking the onset and conclusion of its burst phase

"stability", "design" and "photodynamic therapy" have gained prominence. It is noteworthy that classical research on NAPs continues in the field of cancer, while new research trends have also emerged simultaneously.

3.2.3 Analysis of hot publications

The citation frequency of publications can reflect the significance and referential interest of the research, and often the most initial, representative, and high-quality research is more likely to be cited. Citation frequency can be categorized into global citations, which represent the number of times a publication has been cited across the entire range of the literature database, and local citations, whose citation sources are restricted to the current dataset. Thus, local citations are less frequent than global citations, but more representative of the hotspots in the research field. Here, we shortlist the 10 most global cited and 10 most local cited publications and there main contents (Table 4 and S2-3). The global cited publications all have a citation frequency of 400 or more, and two publications overlap in the two results sets. The most global cited publication is "Database resources of the National Center for Biotechnology Information" [82] published in Nucleic Acids Res, with a total citation frequency of 1219. And the most local cited is "Aptamers evolved from live cells as effective molecular probes for cancer study" published in Proc Natl Acad Sci U S A [83], with a total citation count of 100.

The citation burst refers to a sudden increase in the number of citations of a publication in a certain period of time, which usually suggests the research direction receives extra attention in this timeframe. After filtering, the top 25 citation burst publications are listed in Fig. 7. It can be observed that although research on NAPs began in the 1990s, it was not until around 2013 that hot research commenced to emerge. Since then, almost every year, new studies have been in the limelight, hinting that the research in the field of NAPs is in a period of continuous updating and development. Among the cited bursts screened, the article published in J. Am. Chem. Soc, "A Nonenzymatic Hairpin DNA Cascade Reaction Provides High Signal Gain of mRNA Imaging inside Live Cells" holds the highest strength [84]. Here, Wu et al. report their hairpin DNA cascade amplifier (HDCA), a convenient method that enables mRNA detection inside live cells for the first time.

The latest burst publications often represent some of the current research hotspots. It can be seen that Ma et al. [85] developed a dual-signal platform based on surface-enhanced Raman scattering and upconversion to detect biomolecules in living cells in situ, which enables the universal and ultrasensitive detection of nucleic acids and proteins. Rupaimoole et al. [86] summarised the progress of miRNA therapeutics in oncology in 2017. The use of mimic miRNAs or anti-miRNAs can modulate tumour gene expression and is a promising anti-tumor therapy. Chen et al. [87] reported in Science that RNA-guided DNA binding releases the trans-cleavage activity of Cas12a, which is an indiscriminate single-stranded DNA cleavage. Based on this property, the DNA endonuclease-targeted CRISPR trans reporter (DETECTR) technology was developed to achieve highly sensitive detection at the DNA attomolar level. The same year, Gootenberg et al. [88] published the article "Multiplexed and portable nucleic acid detection platform with Cas13, Cas12a, and Csm6" in Science. There, the authors presented updated advances in the specific high sensitivity entry representative unlocking (SHERLOCK) platform, which utilizes the lateral flow of the CRISPR-Cas13 system to detect liquid biopsy samples from patients with both convenience and reusability.

Table 4 Top 10 most cited documents

No	10 most global cited		10 most local cited	
	Document	Global citations	Document	Local citations
1	Sayers Ew, 2010, Nucleic Acids Res [82]	1219	Shangguan D, 2006, P Natl Acad Sci Usa [83]	100
2	Shangguan D, 2006, P Natl Acad Sci Usa [83]	1194	Ryoo Sr, 2013, Acs Nano [89]	84
3	Kelkar Ss, 2011, Bioconjugate Chem [90]	975	Yin Bc, 2012, J Am Chem Soc [91]	80
4	Lin Yh, 2014, Accounts Chem Res [92]	924	Wu Cc, 2015, J Am Chem Soc [84]	66
5	Wheeler Dl, 2007, Nucleic Acids Res [93]	729	Wu Z, 2015, J Am Chem Soc [10]	58
6	Huang Zw, 2003, Int J Cancer [94]	667	Li L, 2016, Chem Sci [95]	52
7	Liang J, 2015, Chem Soc Rev [96]	634	Tang Zw, 2007, Anal Chem [97]	42
8	Wheeler Dl, 2008, Nucleic Acids Res [98]	623	Prigodich Ae, 2012, Anal Chem [99]	40
9	Banerjee S, 2013, Chem Soc Rev [100]	552	Das J, 2016, J Am Chem Soc [101]	38
10	Yin Bc, 2012, J Am Chem Soc [91]	448	Kam Y, 2012, Mol Pharmaceut [102]	36

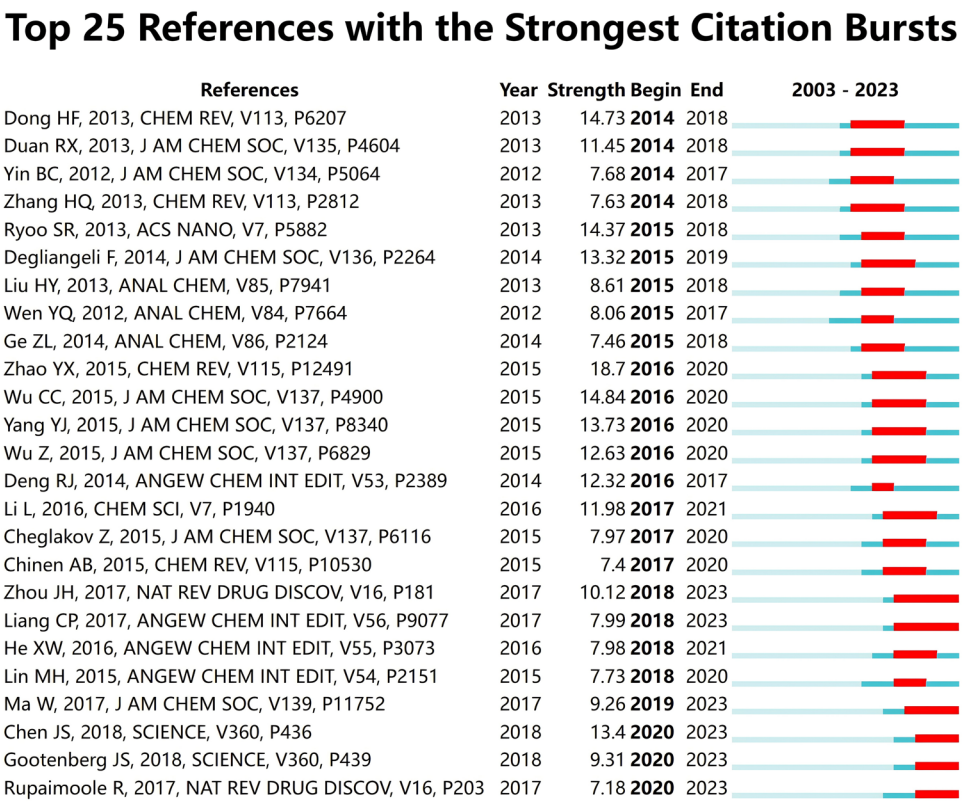

Fig. 7 The top 25 references with the strongest citation bursts

4 Discussion

Over the past three decades, NAPs have undergone rapid development and widespread application, particularly in the diagnosis and treatment of tumors. To comprehensively understand the current state and evolutionary trends in these areas, we conducted a bibliometric analysis.

This study analyzed 13,690 articles on NAPs, with 561 published in 2024 and projections indicating an annual total exceeding 600, highlighting NAP as a dynamic research area. The U.S. and China lead in publication volume, with the Chinese Academy of Sciences being the most prolific institution, while the U.S. has the highest citation rate (55.1 citations/article). The U.S.-China collaboration is the most frequent. NAP research is interdisciplinary, driven by biochemistry and spanning medicine, agronomy, and environmental science.

In its early development, NAP was primarily grounded in traditional life sciences, particularly biochemistry, molecular biology, and microbiology, which experienced the highest intensity of innovation. Early advancements in gene sequencing, gene expression analysis, and molecular interactions positioned molecular biology and biochemistry as foundational for NAP research. These fields not only provided the basis for probe design, synthesis, and characterization but also contributed significantly to understanding disease mechanisms, including those related to cancer, infectious diseases, and genetic disorders. Early applications of NAP in microbiology, especially in pathogen detection and genetic identification, further underscored the prominence of these fields. Meanwhile, the ability to detect specific microbial DNA or RNA sequences marked a pivotal advancement, driving progress in diagnostic microbiology.

In recent years, new interdisciplinary fields have emerged at the intersection of traditional domains, addressing complex societal challenges, technological advancements, and the need for more integrated approaches. Examples include data science, neuroeconomics, and environmental engineering, which combine methodologies and theories from multiple disciplines to tackle global issues. The rise of such fields is largely driven by the increasing complexity of contemporary problems, which cannot be solved within the confines of a single discipline. Technological innovation, shifts in disease patterns, precision medicine, and artificial intelligence further catalyze this expansion. Moreover, academic institutions and funding agencies are increasingly supporting interdisciplinary research to foster innovation and provide comprehensive solutions.

Besides, in oncology-related NAP research, 1999 articles were reviewed. Progress in this subfield has been slower, with annual publications not exceeding 100 until 2016. China and the U.S. dominate, with the Chinese Academy of Sciences leading institutions, followed by Hunan University and Florida State University. This dominance is driven by significant investments in NAP technology and precision medicine policy. [103, 104].

The co-occurrence analysis of NAP in cancer research reveals key terms such as "cancer," "DNA," "nucleic acid," and "probe," indicating a well-established, nucleic acid-based understanding of NAPs in oncology. However, ongoing innovations are steering the field toward new areas of focus. Notably, the integration of NAPs with nanomaterials, especially "gold nanoparticles," signals a paradigm shift, emphasizing the growing role of nanotechnology in enhancing the sensitivity and specificity of NAP-based cancer diagnostics and therapies. The emergence of keywords like "liquid biopsy," "drug delivery," and "antisense" highlights the trend toward practical, application-driven research. "Signal amplification" underscores the continuous efforts to improve NAP sensitivity in cancer detection, while "liquid biopsy" reflects the push for non-invasive, real-time diagnostic tools. The inclusion of "drug delivery" and "antisense" illustrates the expanding use of NAPs not only as diagnostic tools but also as regulators of gene expression, offering potential for more targeted cancer therapies.

Temporal keyword analysis reveals a shift in research focus over the past decade. Prior to 2018, research concentrated on foundational topics such as "gene expression," "PNA", and "hybridization," reflecting core molecular mechanisms and techniques in NAP-based cancer research. In the last five years, however, terms like "nanoparticles," "biosensors," "microRNA," and "signal amplification" have gained prominence, reflecting a growing integration of NAPs with advanced technologies. This shift aligns with broader trends in molecular diagnostics and therapies, particularly in personalized medicine and early cancer detection. The rise of "nanoparticles" indicates a cross-disciplinary approach, combining materials science, nanotechnology, and molecular biology to develop more effective diagnostic and therapeutic tools. The growing prominence of "microRNA" reflects an increasing recognition of small RNA molecules in gene regulation, cancer biomarker discovery, and therapeutic applications. The focus on "signal amplification" highlights the need to enhance NAP sensitivity, which is critical for detecting low-abundance cancer biomarkers and improving clinical outcomes.

Burst analysis identifies emerging research trends in cancer NAPs, with keywords like "stability," "design," and "photodynamic therapy" gaining traction. The emphasis on "stability" underscores concerns about the durability of NAPs in clinical settings, addressing issues of degradation and long-term performance. "Design" reflects efforts to create more efficient, targeted NAPs, optimizing their utility in cancer diagnostics and therapy. "Photodynamic therapy" indicates a rising interest in combining NAPs with light-activated treatments for localized cancer therapy, minimizing side effects. Despite these new developments, traditional NAP methods, such as "gene expression," "cell," and "polymerase chain reaction" (PCR), remain central, underscoring the continued relevance of established technologies in cancer research. This blend of traditional and emerging approaches highlights the dynamic nature of cancer research, where established methods and cutting-edge innovations converge to provide new insights and therapeutic possibilities.

The analysis of hotspot studies further illustrates the development and application trends of NAPs in oncology. Aptamers, nucleic acids (DNA or RNA) that can specifically bind to small molecules or proteins, have shown considerable promise. In 2006, Shangguan et al. [83] introduced a cell-based aptamer selection strategy, employing a ssDNA library containing 52-mer random nucleotides to identify aptamer sequences capable of binding specifically to molecules on the surface of target cells. This method generated aptamers that could serve as molecular probes to distinguish between different cell types. The reliability of the results was verified by using FITC-labeled aptamers in conjunction with monoclonal antibodies to detect CCRF-CEM leukemia cells mixed with normal human bone marrow aspirate cells. The aptamers selectively recognized leukemia cells, demonstrating their potential for clinical diagnostics. Similarly, in 2007, Tang et al. [97] employed SELEX to enrich single-stranded DNA aptamers that could specifically bind to the Ramos tumor cell line. The dissociation constants (Kd) of the aptamers obtained were in the nanomolar range.

In addition to cellular-level tumor identification, a variety of compounds are being explored as targets for tumor recognition. MicroRNAs (miRNAs), due to their regulatory roles in oncogene transcription, are considered effective tumor markers. Sequence-specific NAPs can be used for precise miRNA detection. In 2012, Yin et al. [91] developed a circular amplification method for miRNA detection using duplex-specific nuclease (DSN), an enzyme that cleaves DNA in DNA:RNA hybrid strands. This approach employs DNA NAPs targeting miRNA substrates, which are then hydrolyzed by DSN to release fluorescent signals. The miRNA detection limit achieved by this method is in the femtomolar range, and this amplification technique has become a key method in NAP-based detection.

Given that miRNA levels in living cells are dynamic, their detection in vitro may not fully reflect their true biological state. In 2013, Ryoo et al. [89] combined peptide nucleic acids (PNAs) with graphene oxide to enable precise miRNA detection in living cells. PNAs, which replace the sugar-phosphate backbone of DNA with a polypeptide backbone,

exhibit stronger binding affinity and sequence specificity. The fluorescently modified PNA probe, initially quenched by graphene oxide, is activated in the presence of target miRNA, producing luminescence. This system, capable of multiplexed miRNA detection using different fluorescence tags, achieved a detection limit of 1 pM. Similarly, Li et al. [95] utilized graphene oxide and hybridization chain reaction (HCR) technology for the simultaneous detection of two intracellular miRNAs. This method allows for enzyme-free signal amplification, reducing the detection limit to 0.18 pM and enabling dynamic monitoring of miRNAs.

mRNA, another important molecular marker for tumors, reflects cellular processes and protein translation. In 2012, Kam et al. [102] developed a method for detecting intracellular mRNA using PNA-based molecular beacons targeting the mRNA of the KRAS oncogene. The high selectivity of PNAs allows for differentiation of mismatched mRNAs at the single-base level. In 2015, Wu et al. [84] introduced an enzyme-free signal amplification technique to detect mRNA from manganese superoxide dismutase, a protein associated with tumor malignancy. This cyclic amplification method achieved signal output several times greater than conventional probes, even at low concentrations (500 pM), although the absence of enzymes reduced the reaction rate, which was mitigated by using locked nucleic acids (LNAs) in probe design.

Molecular recognition within cells faces the challenge of efficient probe delivery [105]. Traditional delivery methods rely on cellular endocytosis, which can be unstable and inefficient. However, advances in nanotechnology have opened up new possibilities for intracellular delivery. Spherical nucleic acid (SNA) structures, for example, facilitate efficient nucleic acid entry into cells. In 2012, Prigodich et al. [99] developed a dual reporter nanofluorescent probe based on SNA. This system uses two different probes attached to nanofluorophores to monitor mRNA of interest while simultaneously serving as a control. This approach reduces variability in probe delivery efficiency across different cells. In 2015, Wu et al. [10] combined SNA with HCR signal amplification to achieve ultrasensitive intracellular imaging of mRNA in living cells. The SNA structure, consisting of a gold nanoparticle core, a cationic peptide layer, and a fluorescence-modified NAP shell, allows for efficient recognition and amplification of mRNA targets. Experimental results demonstrated that this system is biocompatible and capable of detecting mRNA in various cell lines with a detection limit as low as the picomolar range.

The development of liquid biopsy has significantly advanced the molecular diagnosis of tumors in recent years. Liquid biopsy refers to the diagnostic technique that involves sampling bodily fluids such as blood, cerebrospinal fluid, saliva, pleural fluid, ascites, and urine, among others. Common biomarkers include circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes [51, 106]. Compared to traditional biopsy, liquid biopsy offers the advantages of being less invasive, more versatile, and easier to perform, which has led to its widespread use in diagnosing a variety of diseases, particularly cancers [107–109]. In 2016, Das et al. [101] developed a ctDNA assay system based on DNA clutch probes (DCPs) using an electrochemical approach. This system can distinguish mutated mitochondrial DNA (mtDNA) from wild-type DNA in blood samples. The method relies on the high selectivity of peptide nucleic acids (PNAs) to differentiate blood DNA after it is single-stranded. Mutant ctDNA is captured by specific PNA-modified nanostructured microelectrodes, which activate the sensor to produce an electrical signal. This approach eliminates the need for enzymes, and its feasibility has been demonstrated in lung cancer and melanoma samples, with a detection limit as low as 0.01%. Undoubtedly, the advancement of liquid biopsy has opened up substantial opportunities for the research and application of nucleic acid probes (NAPs). However, challenges such as the low abundance of target molecules in bodily fluids, the complexity of the liquid environment, and the susceptibility of sample sources to interference remain pressing issues that need to be addressed.

Taken together, these findings underscore the dynamic and evolving nature of research on NAP in oncology, where both fundamental and emerging technologies are continuously being explored. The integration of nanotechnology, advancements in biosensors, and the application of NAPs in novel fields such as drug delivery and photodynamic therapy illustrate the expanding scope of this research. The shift in focus from gene expression and hybridization to nanoparticles, biosensors, and signal amplification reflects a broader trend aimed at enhancing the sensitivity, specificity, and applicability of NAP-based approaches. These developments highlight the potential of NAPs to revolutionize cancer diagnosis and treatment, paving the way for more personalized and effective therapeutic strategies. Moving forward, the application of NAPs in clinical and preclinical settings will remain a persistent trend. Furthermore, significant efforts are being made in the development of novel probes with improved specificity, stability, and multiplexing capabilities. This includes the design of next-generation probes capable of detecting rare biomarkers, as well as probes tailored to specific cancer subtypes or tumor microenvironments.

5 Conclusion

The field of NAPs exhibits continuous evolution, with a significant concentration of research in a few prominent countries and institutions, such as China and the USA. Tumor diagnosis and treatment represent crucial clinical applications for NAPs. Current research primarily focuses on two main directions: the selection of tumor markers and the development of new probe assay technologies, which work together towards precision medicine. Undoubtedly, after 30 years of exploration, NAP technology still holds immense potential for contemporary applications. In the future, closer collaboration is needed to promote and refine the technological advancements of NAPs, fostering cooperation between countries, institutions, and disciplines.

Author contributions Conceptualization was contributed by X.Z., S.W., and Q.X.; X.Z. and H.H. wrote the main manuscript text and prepared the figures; manuscript revision was performed by S.W. and Q.X.; figure revision was done by J.S. and N.Z.; and literature collection was responsible for X.Z. and Y.X. All authors reviewed the manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability Data is provided within the manuscript or supplementary information files.

Code availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

References

1. Seeman NC. DNA in a material world. Nature. 2003;421(6921):427–31.
2. Dai Z, Leung HM, Lo PK. Stimuli-responsive self-assembled DNA nanomaterials for biomedical applications. Small. 2017;13(7):1602881.
3. Tam DY, et al. Photoresponsive self-assembled DNA nanomaterials: design, working principles, and applications. Small. 2019;15(26):e1805481.
4. Zhao Y, et al. Nucleic acids analysis. Sci China Chem. 2021;64(2):171–203.
5. Samanta D, Ebrahimi SB, Mirkin CA. Nucleic-acid structures as intracellular probes for live cells. Adv Mater. 2020;32(13):e1901743.
6. Juskowiak B. Nucleic acid-based fluorescent probes and their analytical potential. Anal Bioanal Chem. 2011;399(9):3157–76.
7. Su X, et al. Nucleic acid fluorescent probes for biological sensing. Appl Spectrosc. 2012;66(11):1249–62.
8. Guo J, Ju J, Turro NJ. Fluorescent hybridization probes for nucleic acid detection. Anal Bioanal Chem. 2012;402(10):3115–25.
9. Krishnan Y, Bathe M. Designer nucleic acids to probe and program the cell. Trends Cell Biol. 2012;22(12):624–33.
10. Wu Z, et al. Electrostatic nucleic acid nanoassembly enables hybridization chain reaction in living cells for ultrasensitive mRNA imaging. J Am Chem Soc. 2015;137(21):6829–36.
11. Keyvani F, et al. A hydrogel microneedle assay combined with nucleic acid probes for on-site detection of small molecules and proteins. Angew Chem Int Ed Engl. 2023;62(21):e202301624.
12. Giesendorf BA, et al. Molecular beacons: a new approach for semiautomated mutation analysis. Clin Chem. 1998;44(3):482–6.
13. Kostrikis LG, et al. Spectral genotyping of human alleles. Science. 1998;279(5354):1228–9.
14. Zhang DY, Chen SX, Yin P. Optimizing the specificity of nucleic acid hybridization. Nat Chem. 2012;4(3):208–14.
15. Franzini RM, Kool ET. Efficient nucleic acid detection by templated reductive quencher release. J Am Chem Soc. 2009;131(44):16021–3.
16. Vet JA, et al. Multiplex detection of four pathogenic retroviruses using molecular beacons. Proc Natl Acad Sci U S A. 1999;96(11):6394–9.
17. Thant YM, et al. Combined locked nucleic acid probes and high-resolution melting curve analysis for detection of rifampicin-resistant tuberculosis in Northern Thailand. Diagnostics (Basel). 2022;12(10):2307.
18. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.

19. Torre LA, et al. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomark Prev. 2016;25(1):16–27.
20. Dolgin E. Cancer's new normal. Nat Cancer. 2021;2(12):1248–50.
21. Dolgin E. Publisher Correction: Cancer's new normal. Nat Cancer. 2022;3(3):372.
22. Sawyers CL. The cancer biomarker problem. Nature. 2008;452(7187):548–52.
23. Li N, et al. A sensitive double antibodies sandwich ELISA for the diagnosis and therapeutic evaluation of cervical cancer. Int J Biol Macromol. 2023;225:1315–22.
24. Diaz-Fernandez A, Ferapontova EE. Electrochemical ELASA: improving early cancer detection and monitoring. Anal Bioanal Chem. 2023;415(18):3831–46.
25. Sarhadi VK, Armengol G. Molecular biomarkers in cancer. Biomolecules. 2022;12(8):1021.
26. Schiffman, J.D., P.G. Fisher, and P. Gibbs, Early detection of cancer: past, present, and future. Am Soc Clin Oncol Educ Book. 2015. p. 57–65.
27. Van Poppel H, et al. Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future. Nat Rev Urol. 2022;19(9):562–72.
28. Vaidyanathan R, et al. Cancer diagnosis: from tumor to liquid biopsy and beyond. Lab Chip. 2018;19(1):11–34.
29. Sala A, et al. Global serum profiling: an opportunity for earlier cancer detection. J Exp Clin Cancer Res. 2023;42(1):207.
30. Zhou H, et al. Liquid biopsy at the frontier of detection, prognosis and progression monitoring in colorectal cancer. Mol Cancer. 2022;21(1):86.
31. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer. 2011;11(6):426–37.
32. El Bali L, et al. Comparative study of seven commercial kits for human DNA extraction from urine samples suitable for DNA biomarker-based public health studies. J Biomol Tech. 2014;25(4):96–110.
33. Jahr S, et al. DNA fragments in the blood plasma of cancer patients: quantitations and evidence for their origin from apoptotic and necrotic cells. Cancer Res. 2001;61(4):1659–65.
34. Breitbach S, et al. Direct quantification of cell-free, circulating DNA from unpurified plasma. PLoS ONE. 2014;9(3):e87838.
35. Song P, et al. Limitations and opportunities of technologies for the analysis of cell-free DNA in cancer diagnostics. Nat Biomed Eng. 2022;6(3):232–45.
36. Jamshidi A, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. Cancer Cell. 2022;40(12):1537–49.
37. Lance RS, Drake RR, Troyer DA. Multiple recognition assay reveals prostasomes as promising plasma biomarkers for prostate cancer. Expert Rev Anticancer Ther. 2011;11(9):1341–3.
38. Hendriks RJ, et al. Comparative analysis of prostate cancer specific biomarkers PCA3 and ERG in whole urine, urinary sediments and exosomes. Clin Chem Lab Med. 2016;54(3):483–92.
39. Hennigan ST, et al. Low abundance of circulating tumor DNA in localized prostate cancer. JCO Precis Oncol. 2019;3:1–13.
40. Crooke ST, et al. RNA-targeted therapeutics. Cell Metab. 2018;27(4):714–39.
41. Li X, et al. Liquid biopsy of circulating tumor DNA and biosensor applications. Biosens Bioelectron. 2019;126:596–607.
42. Chen M, Zhao H. Next-generation sequencing in liquid biopsy: cancer screening and early detection. Hum Genomics. 2019;13(1):34.
43. El-Ashmawy NE, et al. Serum LncRNA-ATB and FAM83H-AS1 as diagnostic/prognostic non-invasive biomarkers for breast cancer. Life Sci. 2020;259:118193.
44. Go AT, van Vugt JM, Oudejans CB. Non-invasive aneuploidy detection using free fetal DNA and RNA in maternal plasma: recent progress and future possibilities. Hum Reprod Update. 2011;17(3):372–82.
45. Batool SM, et al. The liquid biopsy consortium: challenges and opportunities for early cancer detection and monitoring. Cell Rep Med. 2023;4(10):101198.
46. Gerasimova YV, Kolpashchikov DM. Enzyme-assisted target recycling (EATR) for nucleic acid detection. Chem Soc Rev. 2014;43(17):6405–38.
47. Zhu D, et al. Poly-adenine-mediated fluorescent spherical nucleic acid probes for live-cell imaging of endogenous tumor-related mRNA. Nanomedicine. 2018;14(6):1797–807.
48. Ou X, et al. A highly sensitive and facile graphene oxide-based nucleic acid probe: Label-free detection of telomerase activity in cancer patient's urine using AIEgens. Biosens Bioelectron. 2017;89(Pt 1):417–21.
49. Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic—implementation issues and future challenges. Nat Rev Clin Oncol. 2021;18(5):297–312.
50. Lone SN, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. Mol Cancer. 2022;21(1):79.
51. Alix-Panabières C, Pantel K. Liquid biopsy: from discovery to clinical application. Cancer Discov. 2021;11(4):858–73.
52. Botezatu IV, et al. Aberrant methylation scanning by quantitative DNA melting analysis with hybridization probes as exemplified by liquid biopsy of SEPT9 and HIST1H4F in colorectal cancer. Clin Chim Acta. 2023;551:117591.
53. Li D, et al. Progress in the molecular pathogenesis and nucleic acid therapeutics for Parkinson's disease in the precision medicine era. Med Res Rev. 2020;40(6):2650–81.
54. Evers MM, Toonen LJ, van Roon-Mom WM. Antisense oligonucleotides in therapy for neurodegenerative disorders. Adv Drug Deliv Rev. 2015;87:90–103.
55. Shigeto H, et al. Imaging analysis of EGFR mutated cancer cells using peptide nucleic acid (PNA)-DNA probes. Analyst. 2019;144(15):4613–21.
56. Shigeto H, et al. Localization of EGFR mutations in non-small-cell lung cancer tissues using mutation-specific PNA-DNA probes. Cancer Genomics Proteomics. 2023;20(4):375–82.
57. Tadimety A, et al. Design of peptide nucleic acid probes on plasmonic gold nanorods for detection of circulating tumor DNA point mutations. Biosens Bioelectron. 2019;130:236–44.
58. Nafa K, Hameed M, Arcila ME. Locked nucleic acid probes (LNA) for enhanced detection of low-level, clinically significant mutations. Methods Mol Biol. 2016;1392:71–82.
59. Wang MC, et al. Predicting outcomes of EGFR-targeted therapy in non-small cell lung cancer patients using pleural effusions samples and peptide nucleic acid probe assay. Clin Chem Lab Med. 2017;55(12):1979–86.

60. Rigby S, et al. Fluorescence in situ hybridization with peptide nucleic acid probes for rapid identification of *Candida albicans* directly from blood culture bottles. J Clin Microbiol. 2002;40(6):2182–6.
61. Stender H. PNA FISH: an intelligent stain for rapid diagnosis of infectious diseases. Expert Rev Mol Diagn. 2003;3(5):649–55.
62. Kenny JH, et al. Detection of viable *Yersinia pestis* by fluorescence in situ hybridization using peptide nucleic acid probes. J Microbiol Methods. 2008;75(2):293–301.
63. Gu J, Smith JL, Dowling PK. Fluorescence in situ hybridization probe validation for clinical use. Methods Mol Biol. 2017;1541:101–18.
64. Liu G, Zhang T. Single copy oligonucleotide fluorescence in situ hybridization probe design platforms: development, application and evaluation. Int J Mol Sci. 2021;22(13):7124.
65. Price CM. Fluorescence in situ hybridization. Blood Rev. 1993;7(2):127–34.
66. Huang G, et al. The application of nucleic acid probe-based fluorescent sensing and imaging in cancer diagnosis and therapy. Front Chem. 2021;9:705458.
67. Sardaru MC, et al. Nucleic acid probes in bio-imaging and diagnostics: recent advances in ODN-based fluorescent and surface-enhanced Raman scattering nanoparticle and nanostructured systems. Molecules. 2023;28(8):3561.
68. Tian T, et al. Targeted imaging of brain tumors with a framework nucleic acid probe. ACS Appl Mater Interfaces. 2018;10(4):3414–20.
69. Metcalf GA, et al. Amplification-free detection of circulating microRNA biomarkers from body fluids based on fluorogenic oligonucleotide-templated reaction between engineered peptide nucleic acid probes: application to prostate cancer diagnosis. Anal Chem. 2016;88(16):8091–8.
70. Weier HU, et al. FISH in cancer diagnosis and prognostication: from cause to course of disease. Expert Rev Mol Diagn. 2002;2(2):109–19.
71. Metaferia B, et al. Development of peptide nucleic acid probes for detection of the HER2 oncogene. PLoS ONE. 2013;8(4):e58870.
72. Hicks D, et al. Bibliometrics: the Leiden Manifesto for research metrics. Nature. 2015;520(7548):429–31.
73. Ninkov A, Frank JR, Maggio LA. Bibliometrics: methods for studying academic publishing. Perspect Med Educ. 2022;11(3):173–6.
74. Li D, et al. A bibliometric analysis of PROTAC from 2001 to 2021. Eur J Med Chem. 2022;244:114838.
75. Mukherjee D, et al. Guidelines for advancing theory and practice through bibliometric research. J Bus Res. 2022;148:101–15.
76. Hu X, et al. Aptamer-based probes for cancer diagnostics and treatment. Life (Basel). 2022;12(11):1937.
77. Thompson DF, Walker CK. A descriptive and historical review of bibliometrics with applications to medical sciences. Pharmacotherapy. 2015;35(6):551–9.
78. Chen C. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. J Am Soc Inf Sci Technol. 2006;57(3):359–77.
79. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84(2):523–38.
80. Ihaka R, Gentleman R. R: a language for data analysis and graphics. J Comput Graph Stat. 1996;5(3):299–314.
81. Aria M, Cuccurullo C. bibliometrix: an R-tool for comprehensive science mapping analysis. J Informet. 2017;11(4):959–75.
82. Sayers EW, et al. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2010;38(Database issue):D5-16.
83. Shangguan D, et al. Aptamers evolved from live cells as effective molecular probes for cancer study. Proc Natl Acad Sci U S A. 2006;103(32):11838–43.
84. Wu C, et al. A Nonenzymatic hairpin DNA cascade reaction provides high signal gain of mRNA imaging inside live cells. J Am Chem Soc. 2015;137(15):4900–3.
85. Ma W, et al. Dual quantification of microRNAs and telomerase in living cells. J Am Chem Soc. 2017;139(34):11752–9.
86. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov. 2017;16(3):203–22.
87. Chen JS, et al. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science. 2018;360(6387):436–9.
88. Gootenberg JS, et al. Multiplexed and portable nucleic acid detection platform with Cas13, Cas12a, and Csm6. Science. 2018;360(6387):439–44.
89. Ryoo SR, et al. Quantitative and multiplexed microRNA sensing in living cells based on peptide nucleic acid and nano graphene oxide (PANGO). ACS Nano. 2013;7(7):5882–91.
90. Kelkar SS, Reineke TM. Theranostics: combining imaging and therapy. Bioconjug Chem. 2011;22(10):1879–903.
91. Yin BC, Liu YQ, Ye BC. One-step, multiplexed fluorescence detection of microRNAs based on duplex-specific nuclease signal amplification. J Am Chem Soc. 2012;134(11):5064–7.
92. Lin Y, Ren J, Qu X. Catalytically active nanomaterials: a promising candidate for artificial enzymes. Acc Chem Res. 2014;47(4):1097–105.
93. Wheeler DL, et al. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2007;35(Database issue):D5-12.
94. Huang Z, et al. Near-infrared Raman spectroscopy for optical diagnosis of lung cancer. Int J Cancer. 2003;107(6):1047–52.
95. Li L, et al. Two-color imaging of microRNA with enzyme-free signal amplification via hybridization chain reactions in living cells. Chem Sci. 2016;7(3):1940–5.
96. Liang J, Tang BZ, Liu B. Specific light-up bioprobes based on AIEgen conjugates. Chem Soc Rev. 2015;44(10):2798–811.
97. Tang Z, et al. Selection of aptamers for molecular recognition and characterization of cancer cells. Anal Chem. 2007;79(13):4900–7.
98. Wheeler DL, et al. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2008;36(Database issue):D13-21.
99. Prigodich AE, et al. Multiplexed nanoflares: mRNA detection in live cells. Anal Chem. 2012;84(4):2062–6.
100. Banerjee S, et al. Recent advances in the development of 1,8-naphthalimide based DNA targeting binders, anticancer and fluorescent cellular imaging agents. Chem Soc Rev. 2013;42(4):1601–18.
101. Das J, et al. DNA Clutch probes for circulating tumor DNA analysis. J Am Chem Soc. 2016;138(34):11009–16.
102. Kam Y, et al. Detection of endogenous K-ras mRNA in living cells at a single base resolution by a PNA molecular beacon. Mol Pharm. 2012;9(3):685–93.
103. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793–5.
104. Lu Z, et al. The landscape of cancer research and cancer care in China. Nat Med. 2023;29(12):3022–32.

105. Zhu Z, et al. Niosome-assisted delivery of DNA fluorescent probe with optimized strand displacement for intracellular microRNA21 imaging. Biosensors (Basel). 2022;12(8):557.
106. Nikanjam M, Kato S, Kurzrock R. Liquid biopsy: current technology and clinical applications. J Hematol Oncol. 2022;15(1):131.
107. Freitas AJA, et al. Liquid biopsy as a tool for the diagnosis, treatment, and monitoring of breast cancer. Int J Mol Sci. 2022;23(17):9952.
108. Zhang Z, et al. Liquid biopsy in gastric cancer: predictive and prognostic biomarkers. Cell Death Dis. 2022;13(10):903.
109. Li W, et al. Liquid biopsy in lung cancer: significance in diagnostics, prediction, and treatment monitoring. Mol Cancer. 2022;21(1):25.