

APPLIED SCIENCES AND ENGINEERING

Global trends in clinical trials involving engineered biomaterials

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Engineered biomaterials are materials specifically designed to interact with biological systems for biomedical applications. This paper offers the comprehensive analysis of global clinical trial trends involving such materials. We surveyed 834 studies in the ClinicalTrials.gov database and explored biomaterial types, their initiation points, and durations in clinical trials. Predominantly, synthetic and natural polymers, particularly silicone and collagen, are used. Trials, focusing on ophthalmology, dentistry, and vascular medicine, are primarily conducted in the United States, Canada, and Italy. These trials encompass a broad demographic, and trials enrolled fewer than 100 participants. The study duration varied ranging from 0.5 to 4.5 years. These biomaterials are mainly bioresorbable or bioinert, with the integration of cells in biomaterials remaining an underexplored area. Our findings shed light on current practices and future potentials of engineered biomaterials in clinical research, offering insights for advancing this dynamic field globally.

INTRODUCTION

“Engineered biomaterials” refer to materials that are specifically designed and fabricated to interact with biological systems for various applications in medicine, tissue engineering, and regenerative medicine (1–3). These biomaterials are tailored to have specific physical, chemical, and biological properties that enable them to interact favorably with living tissues, cells, and biological processes. The engineering of biomaterials involves careful selection of raw materials and the manipulation of their properties to achieve desired functionalities. These materials can be synthetic, natural, or a combination of both (4). They can be categorized into various classes, including polymers, ceramics, metals, composites, autologous materials, and more. The design and development of engineered biomaterials consider factors such as biocompatibility, bioactivity, mechanical properties, degradation characteristics, and the ability to support cellular adhesion, proliferation, and tissue regeneration (5).

A wide array of biomaterials has found successful applications in various clinical settings (Fig. 1). Earlier, bioinert metals were primarily used for clinical procedures, such as hip and knee replacements, dental implants, and the fixation of bone with plates and screws (6). Overtime, these bioinert materials have been gradually replaced by biocompatible, synthetic polymers for implantation, and vascular grafts. Gradually, bioactive materials were developed, including ceramics such as hydroxyapatite and bioactive glass, which gained popularity as coatings for implants and as graft materials to promote bone growth (7). Specifically, the 20th century saw the introduction of advanced ceramics and alloys for hip and knee replacements, enhancing the durability and performance of these implants

(6). Subsequently, natural polymers such as collagen and alginate have been extensively used for tissue repair, marking a notable shift in biomaterials choices (8, 9). Over the past few decades, biomaterials have undergone remarkable developments, giving rise to personalized implants, smart materials, biohybrids, and bioresponsive substrates (10, 11). Looking ahead, the future of biomaterials promises the emergence of autonomously evolving biomaterials that adapt to their environment and usher in an era of complete biological integration, revolutionizing the landscape of clinical applications.

Biomaterials have a wide range of applications within clinical settings, offering innovative solutions in the fields of tissue engineering, regenerative medicine, and drug delivery systems. These materials play a fundamental role in the development of artificial organs, scaffolds, and implants designed to replace or repair damaged tissues. Many popular biomaterials present a nano-, micro-, or macroporous structure capable of absorbing fluids, trapping and releasing biomolecules, and housing adhered cells. Biomaterials offer mechanical tunability resulting from their selected compositions to mimic the native extracellular matrix of a desired tissue. By providing a supportive framework for cell growth and development, biomaterials facilitate the process of tissue regeneration. In the realm of regenerative medicine, biomaterials enable the precise delivery of growth factors, stem cells, and other therapeutic agents. This controlled delivery system helps stimulate tissue repair and regeneration. For example, in the context of endodontic regeneration, biomaterials serve as scaffolds, providing a platform for delivering stem cells and growth factors to regenerate the pulp-dentin complex.

Emerging biomaterials, such as injectable biomaterials and nanoparticles are at the forefront of biomedical research, promising transformative advances in health care treatments. Injectable biomaterials, including hydrogels, microgels, and in situ curable materials, are extensively used in tissue engineering and drug delivery applications (12–14). These materials are favored for their versatility and minimally invasive application, allowing for precise placement and localized treatment. Hydrogels and microgels, in particular, are engineered to respond to specific physiological conditions, facilitating controlled release of drugs and promoting tissue integration (15). Similarly, in situ curable biomaterials can be delivered in a liquid

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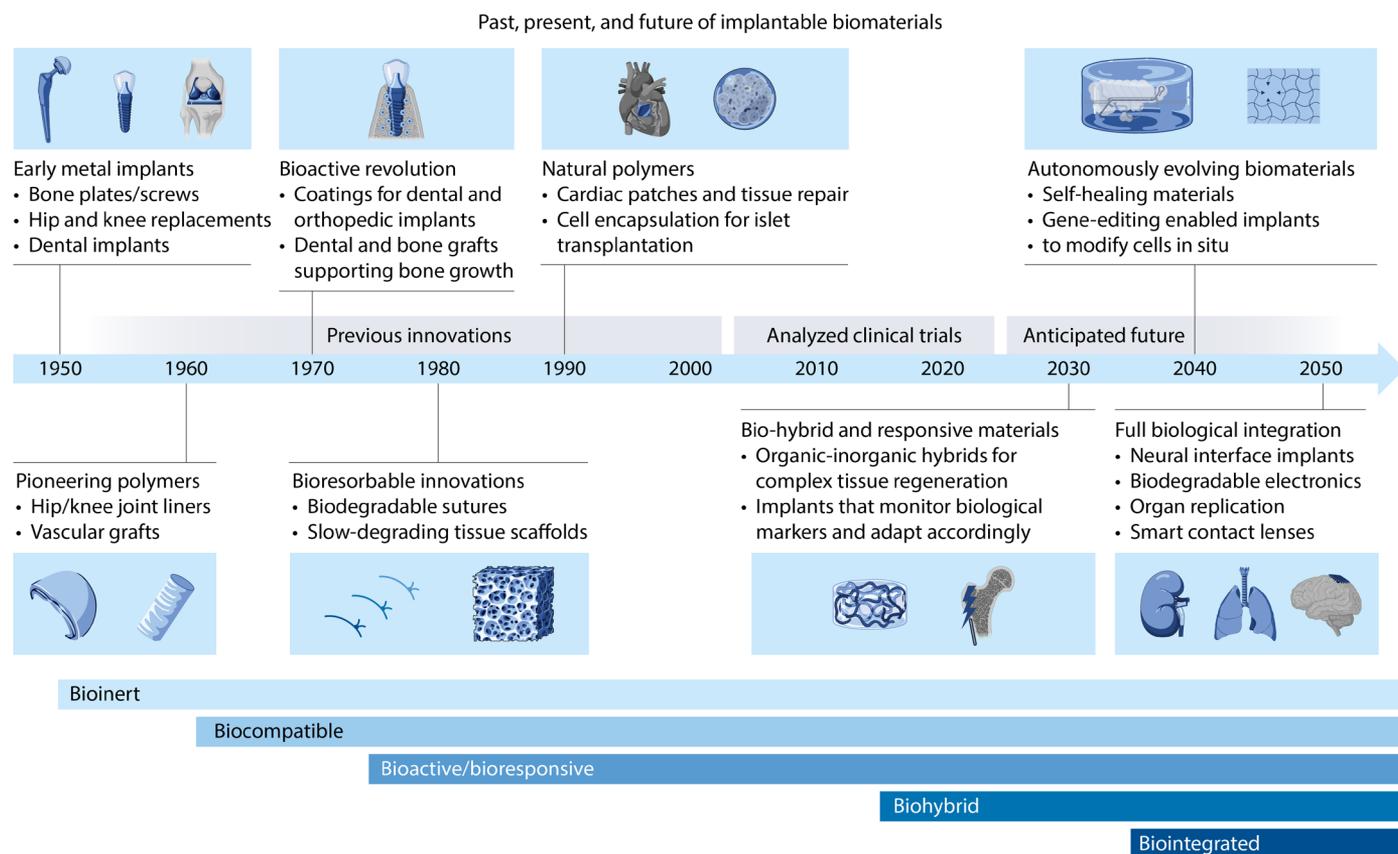


Fig. 1. Evolutionary timeline of implantable biomaterials. This timeline depicts the advancement of biomaterials from the 1950s bioinert metal implants to the envisioned 2050 biointegrated organ replicas. Notable milestones such as biocompatible polymers, bioactive coatings, and future smart implants, predicting a shift toward self-healing materials and organ replication, are marked in the timeline. Figure was created using icons from BioRender.com and modified and finalized in Adobe Illustrator.

state and subsequently solidified directly at the target site, offering structural support and adapting to complex anatomical geometries. These characteristics make injectable biomaterials critical tools in advancing therapeutic strategies and improving patient outcomes in regenerative medicine and targeted drug delivery systems. Nanoparticles similarly enable targeted drug delivery by selectively loading and releasing their cargoes upon interaction with stimuli or through sustained-release profiles (16). These materials effectively encapsulate and transport drugs to specific locations within the body, thereby reducing side effects and enhancing patient compliance.

The development of engineered biomaterials into clinically translated therapeutics relies heavily on effective clinical trials to demonstrate safety and efficacy, as well as to determine appropriate dosages and other parameters. Rigorous evaluation of these materials contributes substantially to advancements in patient care and treatment modalities. Clinical trials, defined by the World Health Organization (WHO) as studies assigning human participants to health interventions for prospective evaluation, play a crucial role globally. They aid in developing safe and effective therapies and vaccines, providing essential data for regulatory approval. The global nature of clinical trials contributes to the advancement of medical research and the availability of innovative treatments worldwide (17–20).

ClinicalTrials.gov is a comprehensive global database maintained by the United States. It offers detailed information on ongoing and completed clinical trials in various medical fields. The database

provides transparency, facilitating access to trial details, participant criteria, and results, which is vital for advancing medical research and informed health care decisions. The high count of clinical trials reflects the numerous efforts made to transition technology from the laboratory to the clinical phase. Numerous prior review articles have focused on trends in clinical trials involving stem cells (21–25), while a select few have examined clinical trials specifically concerning certain biomaterials. For instance, one of the review focused on injectable hydrogels, shedding light on both clinically approved and ongoing investigations in this area (26). Similarly, another review explored the clinical translation of nanomedicine and biomaterials in the context of cancer immunotherapy (27). Another review gathered data from ClinicalTrials.gov to analyze clinical trials related to the therapeutic applications of chitosan (28) and scrutinized trends in clinical trials involving tissue-engineered products in the European Union (29). Here, we aim to broaden our search to encompass the wide range of biomaterials and better understand the distribution of these materials throughout clinical trials.

In the past few decades, a pivotal increase in biomaterials research have yielded enhanced understanding of cell-biomaterials interactions as well as in vivo performance. This knowledge can be used to further improve health care outcomes. Despite increased activity in biomaterials research and their testing in clinical contexts, a thorough analysis of the translation of these biomaterials into clinical applications has not been performed. This study

addresses this gap by analyzing registered clinical trials of biomaterials. The systematic analysis offers a comprehensive overview of biomaterial trials, emphasizing their distribution and highlighting various types of materials used in clinical research. This analysis contributes to a deeper understanding of biomaterial applications in clinical settings.

RESULTS AND DISCUSSION

Given that ClinicalTrials.gov (www.clinicaltrials.gov) stands as the most extensive clinical trials database, we conducted our search on this database using targeted search terms pertinent to engineered biomaterials. We specifically filtered for interventional studies and those that were either completed or actively ongoing but not recruiting

participants. Interventional studies, in contrast to observational ones, generally hold greater clinical relevance as they encompass genuine interventions with human subjects, rendering their findings directly applicable to clinical practice. Among the available options, completed or active but not recruiting studies are more meaningful, offering a more dependable source of information.

In the database search conducted on “ClinicalTrials.gov,” a total of 2767 studies were initially identified using predefined search criteria (Fig. 2). The search terms used included (“nano*”) or (“bio* materials”) or (“hydrogels*”) or (“tissue engineer*”) or (“regenerative medicine”) or (“synthetic materials”) or (“biofabrication”) or (“biopolymers”) or (“bioinspired materials”) or (“biocompatible materials”) or (“nanocomposites”) or (“*scaffold*”) or (“biodegradable”) or (“artificial organs”). We selected these terms to broaden our search of biomaterials

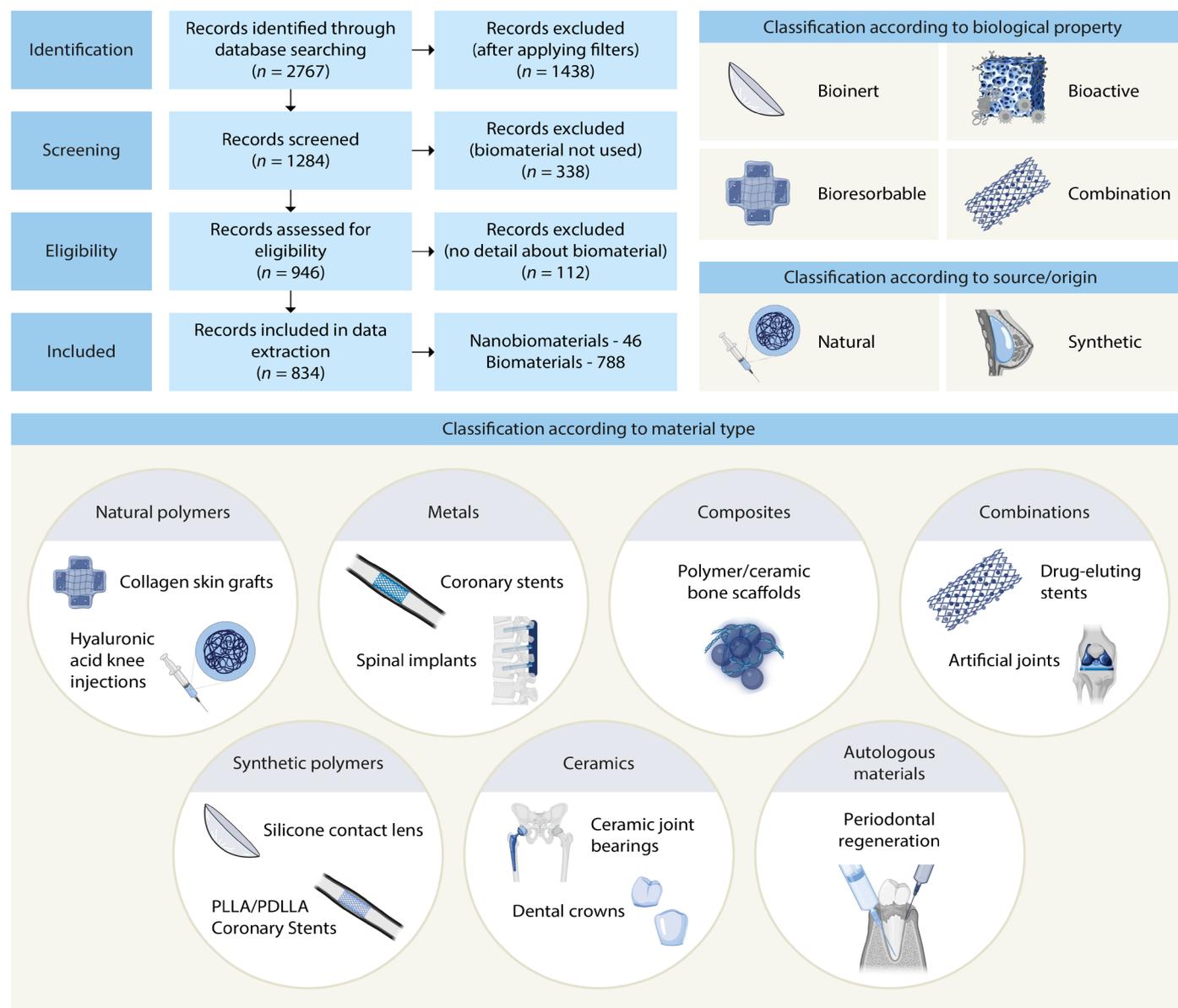


Fig. 2. Flowchart depicting the search process of identification, screening, exclusion, and final inclusion of clinical trials for biomaterials and nanobiomaterials. Figure was created using icons from BioRender.com and modified and finalized in Adobe Illustrator.

and include different types of biomaterials as well as fabrication approaches used to design biomaterials-based devices. Following the application of filters for study status and study type, 1483 studies were excluded, with focus on active, nonrecruiting, and completed interventional studies that were most relevant to biomaterial applications. This resulted in 1284 interventional studies that were further screened for the use of biomaterials across various disease conditions. Within these 1284 studies, 338 were excluded because of the absence of biomaterial use, while an additional 112 studies lacked details regarding the biomaterials used. Consequently, a total of 834 clinical trials involving biomaterials were identified and selected for comprehensive analysis. Among these 834 trials, 788 studies used engineered biomaterials (dataset S1), and 46 studies investigated nano-biomaterials (dataset S2).

Engineered biomaterials are categorized according to three key parameters: their biological properties (bioinert, bioresorbable, and bioactive), their source or origin (natural or synthetic), and their type (polymer, metal, ceramic, autologous, composites, or combinations) (Fig. 2). By classifying engineered biomaterials used in clinical trials based on these characteristics, we can effectively analyze global trends in their application. This systematic approach provides valuable insights into the evolving preferences and technological advancements driving the use of biomaterials in clinical settings.

Bioinert materials are specifically designed to have minimal interaction with biological tissues, rendering them nonreactive and stable when implanted (6). Metals used as implanted biomaterials gain this stability through forming an oxide layer following implantation but retain the ability to integrate with native tissue (6). They are commonly used in medical devices, such as joint replacements or dental implants, to minimize adverse reactions and immune responses from the body. In addition, these materials often present high mechanical strength as appropriate for load-bearing tissues (7). On the other hand, bioactive materials are engineered to actively interact with biological systems, promoting tissue growth, cell adhesion, and other beneficial biological activities (30). This functionality can be affected by the mechanical properties, especially stiffness, of the biomaterial (31). Ceramics are a prominent example of bioactive materials, with their primary application in bone regeneration (32, 33). In contrast, bioresorbable materials are intentionally designed to gradually degrade and be absorbed by the body over time. This unique property makes them ideal for use in scaffolds for regenerative medicine or as temporary medical implants, such as absorbable sutures or even implantable electronics (34, 35).

Engineered biomaterials can be derived from two primary sources: natural, originating from biological organisms and their ecosystems, or synthetic, created via controlled chemical synthesis. Natural biomaterials comprise entities, such as proteins, polysaccharides, and cell-derived matrices, recognized for their inherent compatibility with biological systems. Conversely, synthetic biomaterials are constructed to mimic this compatibility and include products such as silicone breast implants, contact lenses, metal stents, and bioactive ceramics, all tailored for specific medical applications.

Furthermore, the categorization extends to the type of material, which includes polymers, metals, ceramics, autologous, composites, and their combinations. Polymers are split into natural, from biological origins, and synthetic, produced through polymerization. Metals are chosen for their structural properties, while ceramics are inorganic materials. Composite biomaterials were defined as those resulting from the blending of two materials with distinct physical

and chemical properties to enhance the base material's characteristics (e.g., dental composite restorative material). In contrast, a biomaterial was categorized as a "combination" when two materials were combined but not blended, typically serving a specific function, as seen in drug-eluting cardiac stents with a polymer coating on a metal surface for controlled drug release. Autologous material represents a unique category of natural biomaterials where the donor and recipient are the same individual. These materials are considered engineered biomaterials when they are specifically processed to interact therapeutically with biological systems, aligning with our broader definition of engineered biomaterials.

Engineered biomaterials

We analyze the distribution of various biomaterial types—metals, polymers, ceramics, and composites—and assess their initiation points and durations in clinical trials. The data reveal a predominant use of synthetic and natural polymers, especially silicone and collagen, indicative of their broad acceptance.

The predominant biomaterials category used in clinical trials was polymers, which was used in 76% (599) of the studies. Among polymer subtypes, synthetic polymers were the most common, used in 56% (441) of the trials, followed by natural polymers in 20% (156) (Fig. 3). In addition, ceramics and combinations were used in 7.1% (56) and 6.9% (54) of the studies, respectively, while autologous materials were featured in 6% (45) of the trials. Metals and composites were included in 4% of the trials.

In the examination of specific biomaterials within each category, silicone emerged as the predominant material in the synthetic polymer category (Fig. 3), while collagen took the lead in the natural polymer category. Calcium phosphate stood out as the most frequently used material within the ceramic category. In the combination category, both metal and polymer materials were common choices, and platelet-rich fibrin was most prevalent in the autologous material category. Among the metals used, platinum, magnesium, and stainless steel were commonly selected. In the composite category, polymers-ceramics composite were the most used materials.

Synthetic polymers

Synthetic polymers offer advantages in terms of high flexibility in processing, greater economic feasibility, tunable mechanical properties, higher mechanical strength, and improved structural stability. However, they lack inherent bioactivity, may provoke an intense immune response, and require more modifications compared to natural polymers to impart bioactivity. The choice between natural and synthetic polymers depends on specific application requirements, balancing the desired biological response and mechanical performance (36–40). Synthetic polymers were the most commonly used biomaterial, featuring in 441 of the 788 trials with engineered biomaterials. Among these, a total of 53 different materials were used, with silicone (281 trials), Poly(L-lactide) acid (PLLA)/Poly(D, L-lactide) acid (PDLA) (27 trials), poly(ethylene glycol) (PEG, 18 trials), and PLLA (13 trials) being the most prevalent (Fig. 3).

Silicone has emerged as the predominant biomaterials, with the highest volume (281 trials) of research studies across all biomaterial categories. Its primary application lies in the production of contact lenses within the field of ophthalmology. Contact lenses offer effective and safe vision correction to a global population exceeding 140 million individuals. In the United States alone, it is estimated that nearly 1 in 7 Americans, or approximately 45 million people, wear contact lenses (41). The reasons behind the extensive research

Distribution of biomaterials in active clinical trials

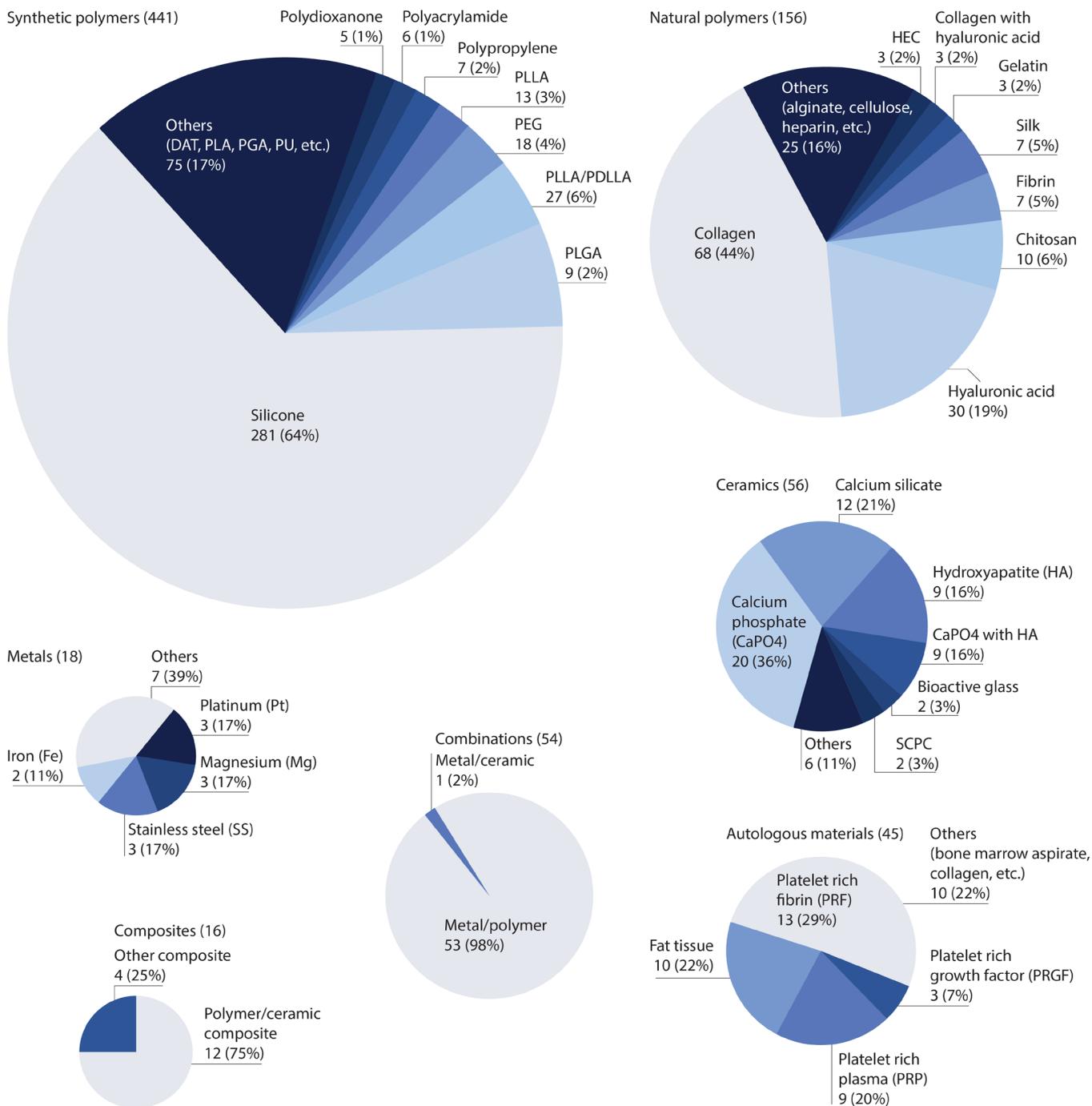


Fig. 3. Distribution of clinical trials involving different biomaterial categories: Synthetic polymers, natural polymers, ceramics, combinations, autologous, metals, and composites.

on contact lenses may stem from several factors, including the large number of contact lens wearers, the feasibility of conducting studies in this population, and the continual introduction of new contact lens products tailored for various usage patterns such as extended wear, daily use, and biweekly or monthly replacement schedules. The 27 trials involving PLLA/PDLLA were exclusively focused on cardiology, investigating fully resorbable cardiac stents. PEG biomaterials

displayed a broader range of applications, spanning ophthalmology, respiratory, and reproductive fields. Among the 13 PLLA studies, more than 50% (7) centered on the evaluation of various PLLA-based cardiac stents.

Natural polymers

Natural polymers have distinct advantages, being inherently bioactive and featuring cell-interactive groups on their backbones. They

offer superior cell attachment, growth, multiplication, and differentiation, with chemically benign degradation products that elicit a low immune response. However, they come with drawbacks, such as difficult processing, lower cost-effectiveness, poor mechanical properties, and the need for cross-linking to enhance strength. Batch-to-batch variations can lead to unpredictable outcomes, and they may lack sufficient mechanical strength while exhibiting hydrophilicity (37–40).

Natural polymers ranked as the second most commonly used biomaterial, featuring in 156 of the 788 engineered biomaterials trials. These trials involved the use of 30 different natural polymers, with collagen (68 trials), hyaluronic acid (30 trials), and chitosan (10 trials) emerging as the most frequently evaluated (Fig. 3). Collagen exhibited a wide range of applications, primarily within dentistry and dermatology. In dentistry, collagen was used for addressing various conditions such as cleft lip and palate, periodontitis, gingival recession, sinus floor augmentation, and immediate implants. Meanwhile, in dermatology, collagen found application in the management of diabetic foot ulcers, burns, skin carcinoma, and open abdominal wounds. Hyaluronic acid had major applications in cosmetics (as a dermal filler for wrinkles, ageing, and correction of volume deficiency in facial regions) and cartilage regeneration (in osteoarthritis). Chitosan was widely used in ophthalmology (for dry eye syndrome) and dentistry (pulpal and periodontal conditions).

Ceramics

Bioceramics, classified as inorganic nonmetallic materials, play a crucial role in bone tissue replacement, leveraging the compositional resemblance of these materials to bone components. Calcium phosphate ceramics (CaPO_4) and bioactive glasses are extensively used as bone substitutes due to their bioactivity and promotion of new bone tissue formation. These biomaterials find broad applications in dentistry, the craniofacial region, and in long bones. Calcium phosphate ceramics come in various forms, including powder and bone cement, with b-tricalcium phosphate (b-TCP) being a commonly used variant. Hydroxyapatite, a calcium phosphate bioceramic, stands out for bone regeneration with its excellent biocompatibility, bioactivity, and bone conductivity, making it a staple in biomedicine and bone defect repair materials. Beyond calcium phosphate, bioactive glass, comprising Na_2O , CaO , SiO_2 , and P_2O_5 , is favored for load-bearing bone repair, thanks to its high bioactivity, bone-binding capacity, and favorable mechanical properties (37, 40).

Of the 56 studies focused on ceramics, the materials most frequently used included calcium phosphate (20 trials), calcium silicate (12 trials), hydroxyapatite (9 trials), the combination of calcium phosphate and hydroxyapatite (5 trials), and bioactive glass (2 trials) (Fig. 3). Calcium phosphate was most commonly applied in bone regeneration (management of long bone fractures, cranial defects, deviated nasal septum, degenerative disc disease, and pseudoarthrosis); all the trials on calcium silicate were in dentistry (alveolar bone loss, furcation defects, pulpitis, jaw atrophy, periodontitis, sinus floor augmentation, and immediate implant placement), while hydroxyapatite was widely used in both dentistry and bone regeneration.

Combinations

The evolution of cardiac stents from bare-metal stents to drug-eluting stents has notably advanced cardiovascular interventions (42–50). Initially, bare-metal stents provided mechanical support after angioplasty, but concerns about in-stent restenosis prompted the development of drug-eluting stents. The drug-eluting stents evolved into three generations based on the properties of the polymer

coating. The first generation of drug-eluting stents, introduced in the early 2000s, featured stainless steel platforms with durable polymer coatings releasing antiproliferative drugs. Second-generation drug-eluting stents, in the mid-2000s, was improved with cobalt-chromium (Co-Cr) or platinum-chromium (Pt-Cr) stent platforms and biocompatible polymers. The third generation of drug-eluting stents, around the 2010s, aimed for reduced restenosis rates, which resulted in the emergence of biodegradable polymer coating, leaving a bare-metal stent by gradual degradation of the polymer and the drug over time.

In this analysis, drug-eluting stents with a metal/alloy platform coated with polymers for drug release have been categorized under the combination biomaterial category. Of the 788 studies considered, 54 of them evaluated biomaterial combinations, particularly involving metal and polymer (Fig. 3). The majority of these trials, numbering 49, focused on cardiac stents. These stents were coated with various polymers, including both durable and bioresorbable varieties, for controlled drug release. Among these, 14 trials explored the use of first- and second-generation drug-eluting stents featuring different platforms (3 stainless steel, 10 cobalt-chromium, and 1 platinum-chromium). A notable portion, 31 trials in total, examined partially resorbable stents constructed from materials like stainless steel (9 trials), cobalt-chromium (17 trials), and platinum-chromium (5 trials). An additional four trials assessed fully absorbable stents constructed from magnesium alloys with polymer coatings.

Autologous materials

Autologous biomaterials, such as platelet concentrates (e.g., platelet-rich-fibrin and platelet-rich plasma) and fat tissue, harness the regenerative potential within a patient's own body. Platelet concentrates contain concentrated growth factors that facilitate tissue healing and are widely applied in fields like orthopedics and dentistry. Fat tissue, obtained through procedures like liposuction, serves as a source of adipose-derived stem cells with versatile differentiation capabilities. These biomaterials are biocompatible, and, as they originate from the patient, minimize the risk of immune rejection (51–54). Among the 45 trials on autologous materials, the top three positions were occupied by platelet-rich-fibrin (13), fat tissue (10), and platelet-rich plasma (9) (Fig. 3). Platelet-rich fibrin found applications in the dental field for the management of gingival recession, pulpitis, alveolar ridge preservation, periodontal attachment, etc. Frequently fat tissue was enriched with adipose tissue-derived stem cells for lipofilling or fat tissue grafts. Platelet-rich plasma was used in the fields of cartilage, dental, and skin for the treatment of osteoarthritis of the knee, regenerative endodontic procedures, periodontitis, and diabetic foot ulcers.

Metals and alloys

Metallic materials are crucial for mechanically supportive components, particularly in applications like repair or replacement of long bones (e.g., femur and tibia) and addressing vertebral bone defects. Ensuring tight bonding to bone is essential for providing physiological load support, but corrosion in the physiological environment can compromise material properties, potentially causing implant failure. Ideal metal materials, exemplified by titanium, magnesium, tantalum, and their alloys, prioritize outstanding biocompatibility, safety, and corrosion resistance. Titanium and its alloys are extensively used in orthopedic implants, yet challenges such as inadequate osseointegration persist. Porous tantalum, known as “bone trabecular metal,” has emerged as a promising alternative due to its

excellent biocompatibility, suitable elastic modulus, corrosion resistance, and high porosity, which facilitates cell adhesion, growth, and differentiation. Implants made of magnesium and its alloys, recognized for their biocompatibility, biodegradability, and osteogenic properties, show promise in fracture fixation. In addition, iron-based alloys are explored for their potential in bone regenerative implants (37, 40).

A total of 18 studies investigated metals (12) and alloys (6) for various applications (Fig. 3). Platinum was used in three clinical trials using coils to treat cerebral aneurysms and gastric varices. Magnesium was examined in two studies for fracture fixation and as a bone screw, and one trial used magnesium as an absorbable cardiac stent. Magnesium and iron-based alloys both served as absorbable cardiac stents, appreciated for their biodegradability. Stainless steel and cobalt-chromium alloys were used as bare metal stents to manage coronary artery disease due to their inertness, biocompatibility, mechanical properties, and radiopacity. Nitinol alloy, known for its superelasticity, was used in a micro catheter. A single trial assessed the safety and efficacy of Ti6Al4V alloy for total shoulder arthroplasty. Tantalum was studied for interbody fusion systems, while zinc was used in a supramolecular active form for treating scalp psoriasis. Radio-labeled indium was analyzed in radio-guided lymph node dissection, and an aluminum hydrogel was evaluated as a drug-delivery vehicle for administering glutamic acid dehydrogenase in the treatment of diabetes mellitus.

Composites

Composite biomaterials are formulations derived from the integration of two or more distinct materials, capitalizing on the strengths of each constituent phase. This category differs from the combination biomaterials category in that composites take advantage of the synergy between the component materials, while combination materials allowed each component material to function independently. In dentistry, for instance, composite materials that amalgamate as a resin matrix with ceramic filler particles are extensively used as restorative materials. This composite design harnesses the advantages of both phases: The organic resin matrix facilitates material adhesion to the tooth, while the filler component enhances the mechanical and physical properties of the resin matrix (37, 40). A total of 16 trials explored the applications of various composite materials, particularly in the realms of bone regeneration and dental care for restorations and craniofacial bone regeneration (Fig. 3). The predominant approach in most of these trials involved combining polymers with ceramics. Both natural and synthetic polymers were blended with various ceramic materials such as calcium phosphate and hydroxyapatite. Some of the polymers used included collagen, gelatin, hyaluronic acid, and PLGA. In dentistry, the composite materials featured a resin matrix comprising Bis-GMA/TEGDMA and silica as the ceramic filler particles.

Global distribution of clinical trials

Single-center clinical trials, conducted within a specific hospital or clinic, offer advantages such as cost-effectiveness and ease of funding compared to multicenter trials. These trials, typically small in scale, provide a conducive environment for clinicians and scientists to innovate and explore new treatments, serving as a valuable source of therapeutic ideas. However, challenges arise when these trials recruit too few participants, risking scientific validity and the possibility of overlooking treatment differences. Relying on a single source for participants may limit the trial size, emphasizing the

need for early recognition of feasibility issues, whereas a multicenter trial is a single trial conducted according to a single protocol but at more than one site according to WHO. These sites may be across multiple countries. Multicenter studies play a crucial role in clinical and public health research, offering advantages such as accelerated recruitment, diverse population representation, and increased generalizability. Despite these benefits, they face methodological, implementation, and statistical challenges that can affect study validity. Effective coordination between centers and study governance mechanisms is essential for successful implementation, along with transparent communication to foster productive collaboration among investigators (55–59).

Among the 834 trials included in the analysis, the majority, 788 (94%) studies, used engineered biomaterials (described in the previous sections), while 46 (6%) focused on nanobiomaterials. The studies were classified as either single-center or multicenter trials based on the number of study locations (Fig. 4). Most of the engineered biomaterials trials, comprising 82% (648 of 788), were conducted as single-center trials, with 10% (77 of 788) falling into the multicenter category, while 8% (63 of 788) lacked specified locations. The multicenter trials encompassed a range of 2 to 25 countries. Among the 77 multicenter trials, a substantial majority (69%, 53 of 77) involved 2 to 4 countries, while 31% (24 of 77) were conducted in 5 to 9 countries. Notably, one trial engaged 263 participants across 10 countries, and another, serving as a continuation of the clinical evaluation of the ABSORB bioresorbable vascular scaffold system for coronary artery lesions, spanned 25 countries and included 812 participants.

Several single-center and multicenter trials failed to meet expectations, with instances of single-center trials having higher enrollment than some multicenter counterparts. A noteworthy single-center trial conducted in Istanbul, Turkey enrolled an impressive 9169 female patients to investigate the short-term effects of transdermal estrogen therapy (which was delivered through the transdermal patch made of synthetic polymer polyacrylate) on postmenopausal women with COVID-19. In contrast, a multicenter trial conducted in Brazil and Poland recruited merely seven patients for a pilot study assessing the Fantom bioresorbable scaffold in coronary artery lesions.

Both single-center and multicenter trials are conducted across multiple countries (Fig. 4B). In single-center trials, the United States emerged as the predominant contributor, with Canada and Italy occupying the second and third positions, respectively. However, in the multicenter trials, Germany and Belgium were in the first and second positions, respectively, with the United States in the third position. In single-center trials, several countries exhibited a strong focus on the investigation of synthetic polymers, with the highest contributions coming from the United States, Canada, China, the UK, France, and Switzerland. In contrast, Italy, Spain, and Brazil emerged as leaders in exploring natural polymers in this context. Egypt, unlike the other countries, primarily explored ceramics in its trials. Among the top 10 countries conducting the multicenter trials, 8 countries were from the European Union, and all the top 10 countries conducted the highest number of trials on synthetic polymers.

Target tissues and diseases in clinical trials

Biomaterials have been explored for the treatment of diverse diseases across multiple organ systems (Fig. 5A). Consequently, we conducted an analysis of the engineered biomaterials clinical trials with respect to the specific diseases under consideration. Among

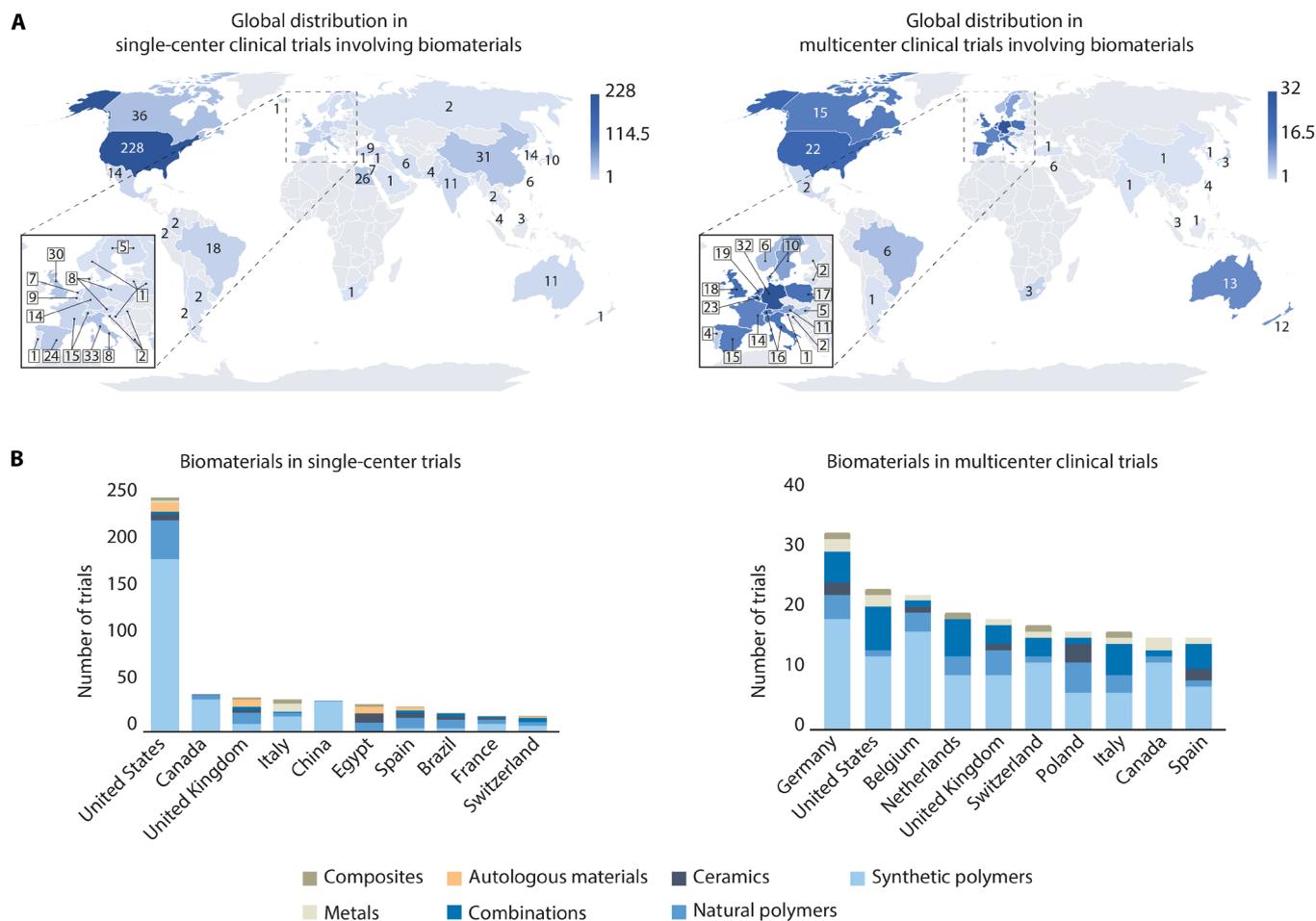


Fig. 4. Geographic distribution of studies involving biomaterials. (A) Global distribution of all clinical trials involving biomaterials in single-center and multicenter trials. (B) Distribution of all clinical trials involving biomaterials in the top 10 countries in single-center and multicenter trials.

the targeted diseases, ophthalmic conditions were the subject of the highest number (310 of 788, 39%) of clinical trials, followed by diseases of blood vessels and the oral cavity (111, 14% each) (Fig. 5, B and C). Collectively, trials concentrating on ophthalmic diseases, coronary artery disease, and conditions affecting the oral cavity comprised a substantial 67% of clinical trials. When categorizing the target diseases, it was necessary to distinguish “blood vessel/stent” from “blood vessel” due to the frequent use of various types of stents in the management of coronary artery disease. However, in the treatment of other blood vessel diseases, stents were not commonly applied. Similarly, in classifying oral cavity diseases, “bone/dental” was separated as the materials used for alveolar bone regeneration differed from those used in other conditions such as pulpitis and periodontitis.

In our analysis of clinical trials, it was observed that synthetic polymers were extensively used in the fabrication of contact lenses for the treatment of ophthalmic diseases (Fig. 5, C and D). Natural polymers were commonly used in addressing skin diseases. Dental applications had seen widespread use of autologous biomaterials, ceramics, and composites. Meanwhile, metals and combination materials, such as polymers coated on metals, were prevalent in the construction of cardiac stents for treating coronary artery disease.

Age, gender, enrollment, and study phase

Ensuring diversity in clinical trials is vital for representative results and understanding potential barriers to disease treatment or therapeutic administration. Factors like socioeconomic status, education, and income correlate with disease prevalence and treatment responses. Age-related changes in organ function and body composition underscore the importance of including older adults in trials. Recognizing gender differences is crucial as they influence disease prevalence, drug response, and adverse reactions. Despite historical underrepresentation, recent data suggest improved gender balance in clinical trials. Addressing these considerations is key for accurate and inclusive clinical research (60). Population variations in disease pathophysiology and local clinical management can lead to inter-ethnic differences in the efficacy or safety profiles observed in drug trials.

Notably, in our analysis, we found that the clinical trial database often lacks clear details regarding race and ethnicity. Well-defined racial/ethnic groups allow for studying disease uniqueness and differences in treatment tolerability and response (61). Examining more than 20,000 US clinical trials reported that only 43% mentioned any race/ethnicity data from March 2000 to March 2020 (62). Recent analyses of COVID-19 clinical trials with remdesivir

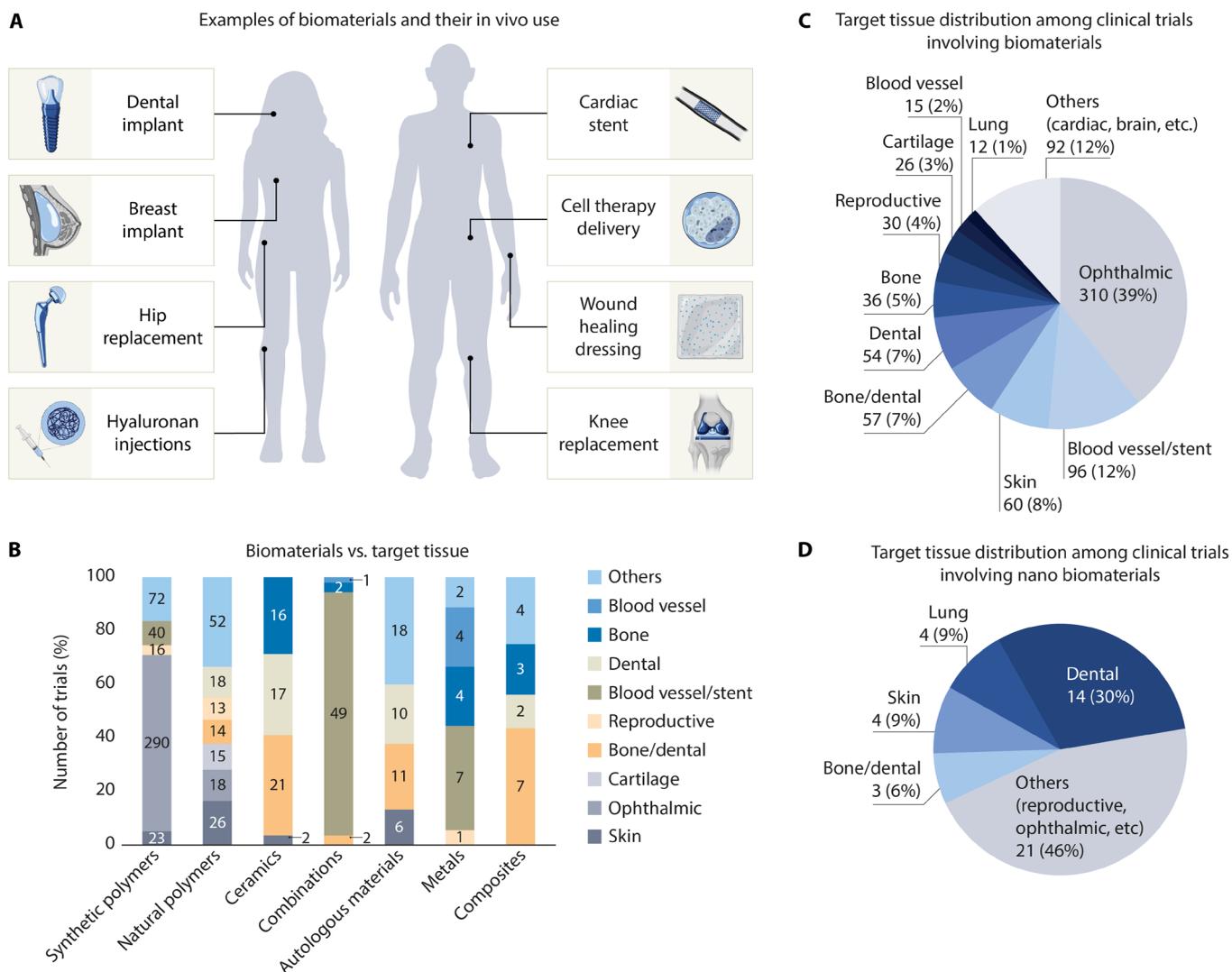


Fig. 5. Disease categories targeted in clinical trials involving biomaterials. (A) Examples of biomaterial applications in disease categories/target tissue. (B) Distribution of clinical trials involving biomaterials in the disease categories (top 10 shown in the graph). (C) Distribution of clinical trials involving biomaterials in various target tissues. (D) Distribution of clinical trials involving nanobiomaterials in various target tissues. Figure was created using icons from BioRender.com and modified and finalized in Adobe Illustrator.

highlighted inadequate representation of Black, Latino, and Native American populations, undermining the reliability of findings (63). To address this, the authors recommended that COVID-19 trials should include marginalized communities, especially Black, Latinx, and Native American populations, to ensure equitable representation and meaningful outcomes (63).

Age or age group as described in the glossary of ClinicalTrials.gov is a type of eligibility criteria that indicates the age a person must be to participate in a clinical study. This may be indicated by a specific age or the following age groups: child (birth to 17), adult or young adult (18 to 64), and older adult (65+). The majority of trials (531, 67%) included participants from both adult and older adult age groups, with 20% (154) of trials exclusively enrolling adults. Only 2% (16) of trials focused on children as their study population. All the age groups (child, adult, and older adult) were involved in 72 (9%) studies (Fig. 6A). Of the trials involving both adults and older adults, 51% (270 of 531) of these focused on the ophthalmic and

blood vessel/stent categories. Among the studies involving only adults, a notable portion (82 of 154) concentrated on ophthalmic conditions, particularly regarding contact lenses. Exclusive pediatric participation was observed in studies related to conditions like cleft lip and palate, various stages of dental caries, periodontitis, and long bone fractures.

A substantial number of trials (94%, 744) enrolled both male and female participants, with 4% (31) recruiting solely females and 2% (13) enrolling only males (Fig. 6B). The female-exclusive trials primarily revolved around research on female reproductive organs (ovary, uterus, vagina, breast, etc.). Trials exclusively involving males were primarily associated with research on the male reproductive organ (prostate) and other areas such as dental health, nerves, cartilage, and inguinal hernia.

On the basis of the study's objective and the number of participants, the Food and Drug Administration (FDA) has categorized the clinical trials on drug or biological products into four phases

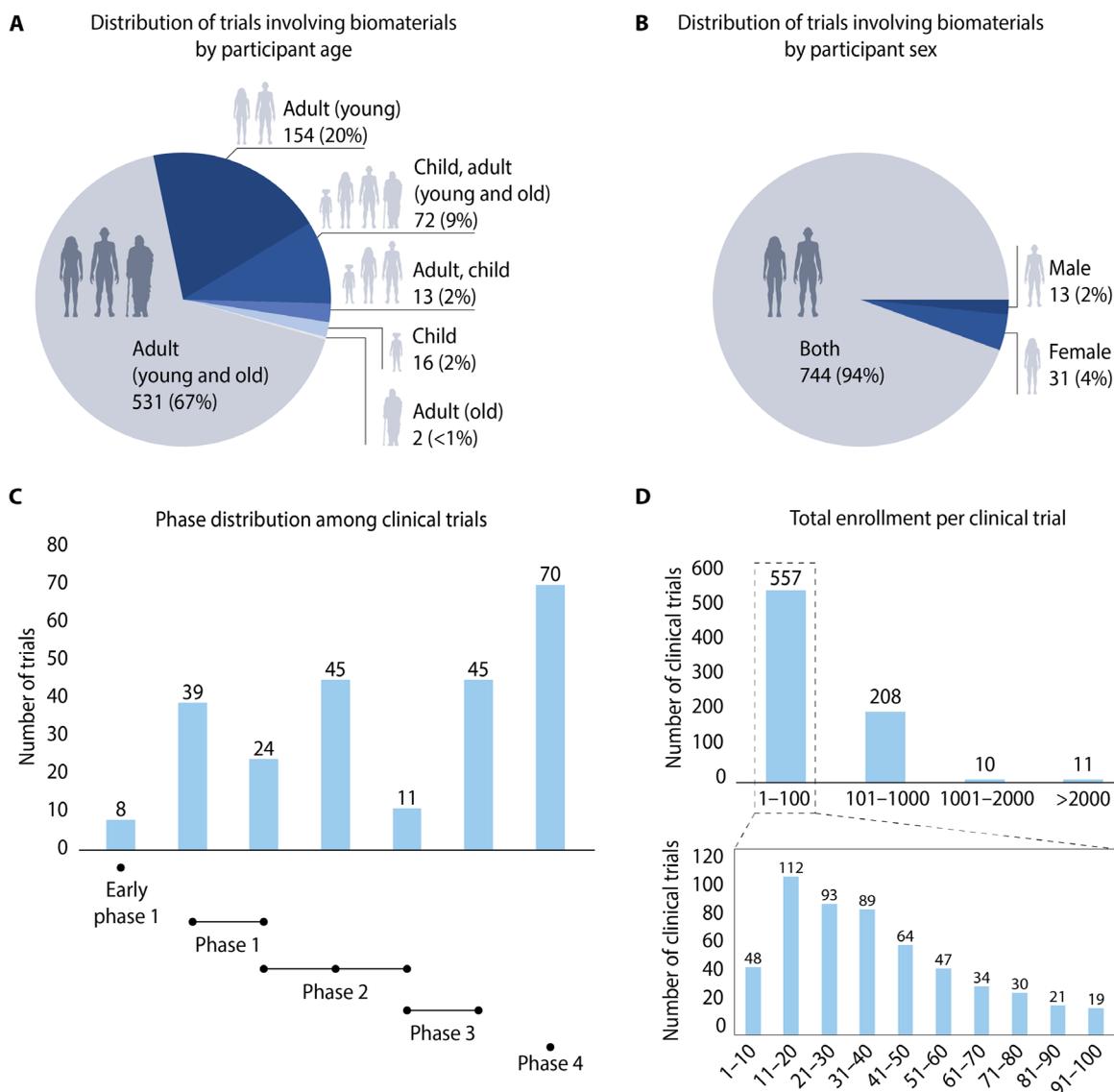


Fig. 6. Age, sex, clinical phase, and enrollment. (A) Distribution of trials involving biomaterials by participant age: child (birth to 17), adult or young adult (18 to 64), and older adult (65+). (B) Distribution of trials involving biomaterials by participant gender. (C) Distribution of clinical trials involving biomaterials in different clinical phases. (D) Distribution of clinical trials based on the range of participants enrolled.

(phases 1 to 4). Phase 1 or “First in Human” trials assess safety in a small group; phase 2 or “Safety and Efficacy” trials examine efficacy and safety in a larger group; phase 3 or “Pivotal” trials investigate efficacy in large human cohorts, comparing to standard or experimental interventions; and phase 4 trials or “Post-Market Surveillance” monitors the approved intervention’s effectiveness and gathers information on widespread use and potential adverse effects following market release. The category “Phase Not Applicable” describes trials without FDA-defined phases, including trials of devices or behavioral interventions. In our study, we explored the progression of biomedical clinical trials through these four phases, focusing on how engineered biomaterials are integrated and evaluated at each stage, from initial safety assessments in phase 1 to post-market surveillance in phase 4.

The majority of the clinical trials (546 of 788, 69%) were categorized as Phase Not Applicable, which describes clinical trials without

FDA-defined phases or trials on devices. Among these, 52% (282 of 546) of the studies were on contact lenses (ophthalmology). As The U.S. FDA regulates all contact lenses as prescription medical devices, the trials on contact lenses (synthetic polymer-silicone) have been categorized as Phase Not Applicable.

In terms of the clinical study phase, 70 studies (9%) fell into phase 4, while 45 studies (6%) were categorized under both phase 2 and phase 3, and 39 studies (5%) were designated as phase 1 (Fig. 6C). Typically, phase 4 trials enroll a substantial number of participants, often exceeding 200, and extend over a duration of 1 to 4 years, as outlined by the US FDA and National Institute of Aging Glossary. However, our analysis revealed that a majority, 70% (49 of 70), of phase 4 trials included fewer than 200 participants. Within this subset, only 30% featured more extensive participant numbers, with merely 13% (9 trials) involving more than 1000 patients. The study duration varied, with 63% (44 of 70) lasting between 1 and 4 years,

while 13% (9 trials) had a duration of less than 1 year, and 24% (17 trials) extended beyond 4 years. Among the 70 studies in phase 4, one-third (26 of 70) focused on cardiac stents. Notably, fully resorbable polymer-based stents, such as ABSORB (PLLA/PDLLA), were prominent biomaterials that had advanced to the final clinical trial phase after FDA approval.

For data collection, the trials were categorized on the basis of the range of participants enrolled. The majority (71%, 557 of 788 studies) included 1 to 100 participants, with a notable portion (14%, 112 trials) enrolling between 11 and 20 patients (Fig. 6D). Conditions involving 11 to 20 patients were most common in studies related to diseases of the oral cavity and ophthalmic health. Of the 21 trials enrolling more than 1000 participants, most focused on coronary artery disease evaluation in the context of cardiac stents. Two studies with more than 1000 female patients were centered on female reproductive organs. One notable instance involved a study conducted in Istanbul, Turkey, which enrolled 9169 female patients, to investigate the short-term effects of transdermal estrogen, which was delivered through the transdermal patch made of synthetic polymer polyacrylate on postmenopausal women with COVID-19.

Study duration of clinical trials

The average trial duration for investigations involving different biomaterials was determined on the basis of the start and end dates (Fig. 7). The search and data extraction processes were conducted in August 2023. During this period, all studies, except for 47, had reached completion. These 47 studies were categorized as “not recruiting but active” due to their extended follow-up. This means that the studies are ongoing, and participants are currently receiving interventions or undergoing examinations, but no new potential participants are being recruited or enrolled. Figure 6B displays studies with the minimum and maximum durations in each biomaterial category. The shortest study, lasting only 4 days, involved natural polymer gelatin in the form of a cream to test skin hypersensitivity. On the other end of the spectrum, the longest study, spanning 12.6 years (4627 days), focused on the treatment of simple coronary bifurcation lesions using the Absorb or Desolve bioresorbable scaffold or stent. The study, which has the latest projected date of completion (September 2029), compares the human acellular vessel with arteriovenous fistula when used for hemodialysis access. The duration of studies within each category varied, with an average ranging from 0.5 years (focused on silicone for contact lenses) to 4.5 years, exploring cardiac stents composed of combination materials involving metal coated with polymers for drug release. The 47 ongoing studies, categorized by biomaterial types, included 20 in the synthetic polymer category, 9 in the natural polymer, 11 in the metal/polymer combination, 4 in the metal, 2 in the autologous, and 1 in the ceramic category. Notably, all the trials on composite materials had been completed by August 2023. Of these 47 studies, 35 are conducted as single-center trials, with the remaining 12 as multicenter trials.

Biomaterial characteristics

Biomaterial properties play a crucial role in their application for medical purposes (Fig. 8A). Bioresorbable biomaterials have the ability to degrade over time within the body, eliminating the need for surgical removal. Bioinert biomaterials, like certain metals and polymers, do not elicit a prominent biological response, minimizing the risk of adverse reactions. On the other hand, bioactive biomaterials promote specific biological interactions and encourage cellular responses

for tissue integration. These properties determine the suitability of biomaterials for various medical applications, from implants to drug delivery systems, based on their intended function and the body's response to the material. The most prevalent biomaterial property was bioresorbability, which was observed in 46% (364) of the trials (Fig. 8B). Following this, bioinert materials were used in 38% (297) of the trials. Bioactive materials, on the other hand, were comparatively less common and featured in only 8% (64) of the studies. In cases of combination and composite materials, properties were expressed as a combination, such as bioinert/bioresorbable or bioresorbable/bioactive.

The bioresorbable materials were predominantly applied in diseases of the oral cavity, blood vessels, and skin. Among the 297 studies investigating biomaterials with bioinert properties, 279 focused on contact lenses made of synthetic polymer silicone, specifically in the field of ophthalmology. The 64 studies involving biomaterials with bioactive properties frequently used ceramic materials (such as calcium phosphate, calcium sulfate, and hydroxyapatite) for applications in dentistry and bone regeneration. In 46 studies with biomaterial properties categorized as bioinert/bioresorbable, 41 centered on cardiac stents, combining metal and polymer materials to contribute the bioinert and bioresorbable properties, respectively. The bioinert materials or alloys used included stainless steel, cobalt-chromium, or titanium, while bioresorbable polymers facilitated drug release. Ten studies on composite materials with combined bioresorbable and bioactive properties integrated polymers and ceramics, finding applications in bone and cartilage regeneration.

Cell-loaded engineered biomaterials

Stem cell-based tissue engineering holds remarkable promise for tissue regeneration and the replacement of damaged organs. The unique features of stem cells, including their ability to self-renew and differentiate into various cell types, make them an attractive choice for therapeutic applications. However, the translation of stem cell research from animal models to human applications presents a challenge, requiring a comprehensive understanding of the underlying mechanisms. Furthermore, addressing immune rejection is crucial for the success of stem cell transplantation, necessitating innovative strategies to overcome this obstacle in clinical settings (64–68). The majority of trials (742, 94%) did not incorporate cells into their studies. In contrast, only a small percentage (46, 6%) of studies used cells in conjunction with biomaterials.

Nanomaterials

Nanobiomaterials, at the intersection of nanotechnology and biomaterial science, are engineered to capitalize on the unique properties afforded by the nanoscale. These materials are extensively used across a range of biomedical applications including drug delivery, diagnostics, imaging, and tissue engineering. Their diminutive size facilitates precise molecular and cellular interactions, which enhances targeted therapeutic delivery and intervention. Furthermore, the nanodimension of these materials greatly improves biocompatibility by mimicking the extracellular matrix, thus promoting better cell adhesion and proliferation. In addition, by optimizing the size, shape, and surface characteristics, nanobiomaterials are designed to evade cellular autophagy pathways, increasing their functional lifespan within the body. This scale also increases the surface area relative to volume, which can be leveraged to improve drug loading capacities and release kinetics, thereby enhancing the performance

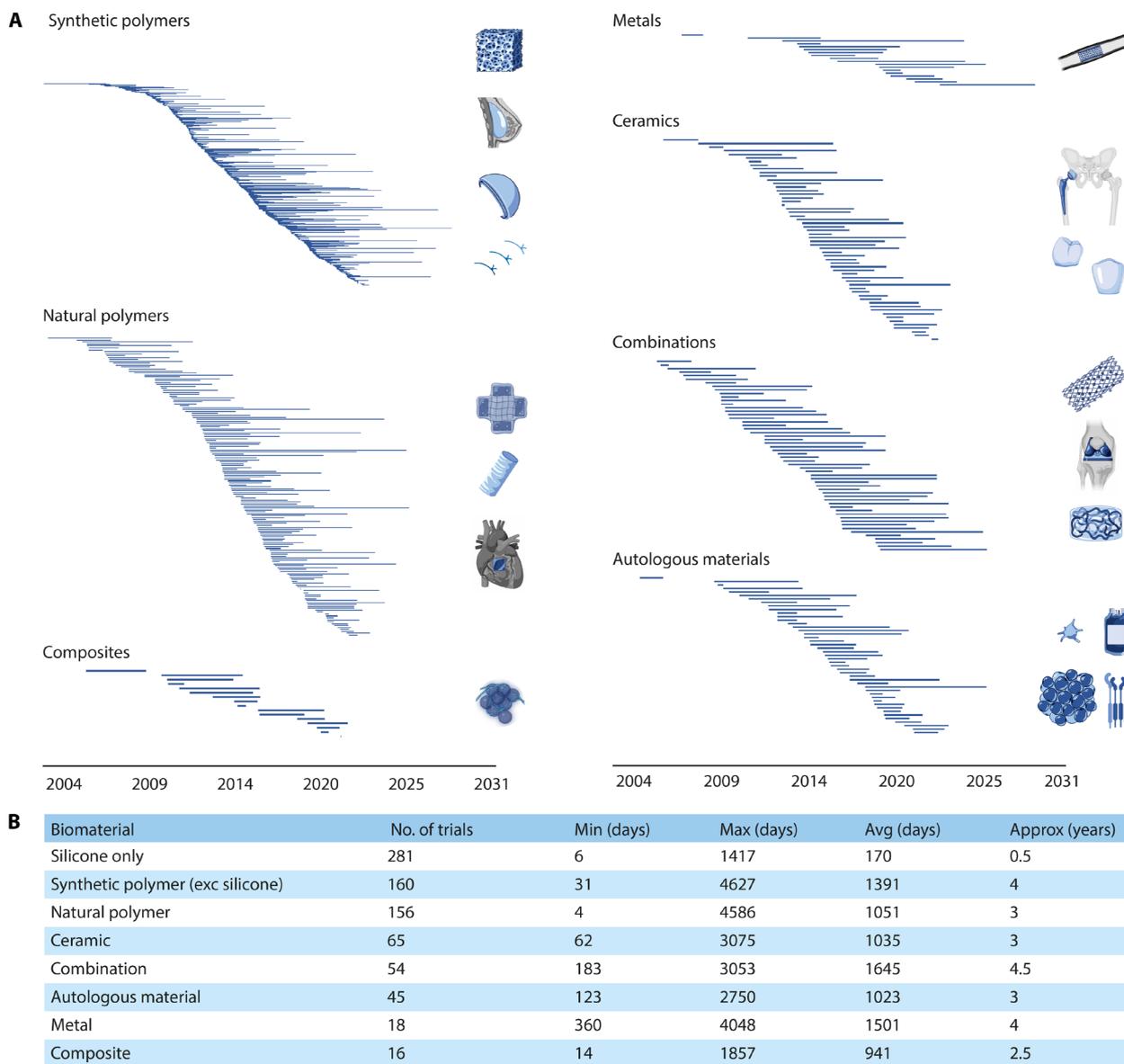


Fig. 7. Study duration of clinical trials. (A) Gantt charts depicting the starting point and the scheduled study duration dependent on the various biomaterial categories. Different plots represent various engineering biomaterials, while each horizontal bar within these plots represents a clinical trial, depicting the start and end dates of the study. (B) Table showing the average duration of clinical trials with minimum and maximum number of days. Figure was created using icons from BioRender.com and modified and finalized in Adobe Illustrator.

of medical devices. Detailed discussions on these mechanisms have been included to illustrate how nanosizing specifically contributes to advanced medical applications.

Among the 834 trials included in the analysis, the majority, 788 (94%) studies, used engineered biomaterials, while 46 (6%) focused on nanobiomaterials. All 46 nanobiomaterial studies were single-center trials, and their global distribution was highest in Egypt (11, 24%), followed by the United States (8, 17%) and Brazil (4, 9%). These nanomaterials found the most application in dentistry (14, 30%), followed by lung (4, 9%) and skin (4, 9%) (Fig. 4D) treatments. Approximately 50% (24 of 46) of the trials recruited both young and older adults, with 30% (14) exclusively enrolling young adults and 9% (4) focused on children. Both genders were

included in 87% (40) of the studies, while only females were involved in 13% (6) of the trials. The majority (72%) of the studies had participant counts ranging from 1 to 100. Regarding the clinical trial phase, only one trial (2%) was in phase 4. Forty-one % of the trials did not specify the phase, and 35% were categorized as phase 2, followed by phase 3 (13%) and phase 1 (9%).

In terms of biomaterial types, an equal distribution was observed between natural and synthetic nanobiomaterials. Depending on their application, these nanobiomaterials were classified on the basis of their material composition as nanodrugs, nanodrug delivery, nanocomposites, nanopolymers, or nanoceramics. These materials were predominantly used in dentistry. Various nanomaterials were used in different categories,

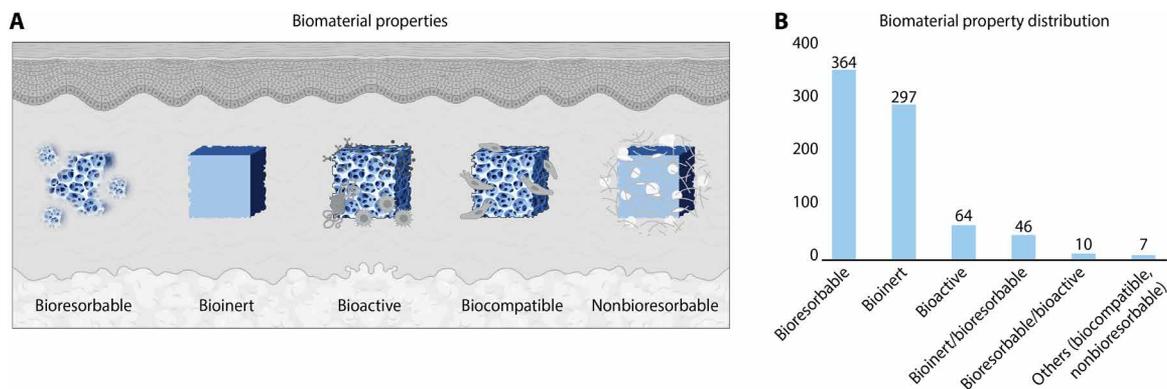


Fig. 8. Distribution of biomaterials in clinical trials based on their physiological stability. (A) Graphical representation of various biomaterial properties such as bioresorbable, bioinert, bioactive, biocompatible, and nonbioresorbable. (B) Distribution of clinical trials involving biomaterials based on the properties. Figure was created using icons from BioRender.com and modified and finalized in Adobe Illustrator.

such as nanohydroxyapatite (nanoceramic), glycidyl methacrylate + silica (nanocomposite), silver nanoparticles (nanodrug), nano albumin (nanodrug delivery), and nano chitosan (nanopolymer). The majority of the materials used were bioactive (37, 80%), followed by bioresorbable (6, 13%), and bioinert (2, 4%). Notably, none of the studies incorporated cells into their applications.

Upon conducting an in-depth analysis of biomaterials and their applications, it becomes evident that they encompass a wide array of materials used across various medical contexts. Natural polymers like collagen and hyaluronic acid have gained distinctive attention in skin care and dermal filler applications due to their biocompatibility and ability to mimic the extracellular matrix, promoting tissue regeneration. In addition, hyaluronic acid has found use in treating knee osteoarthritis, where its viscoelastic properties provide lubrication and cushioning to joints. Synthetic polymers such as silicone are widely used in contact lenses due to their optical clarity and oxygen permeability. Fully resorbable polymers like PLLA/PDLLA have revolutionized coronary stent technology, offered temporary scaffolding while promoted vessel healing without long-term foreign body presence. Metals like magnesium (Mg) have emerged as promising candidates for fully resorbable coronary stents, with the potential benefits of reduced inflammation and long-term complications compared to permanent metallic stents. Combinations of metal platforms with polymer coatings have been developed to enhance the biocompatibility and drug-delivery capabilities of coronary stents, improving patient outcomes. In dentistry and bone regeneration, autologous materials, ceramics, and composites are used to repair and regenerate bone tissue, offering tailored solutions based on patient needs and site-specific requirements. Overall, the current literature highlights the versatility and advancements in biomaterials, demonstrating their crucial role in addressing diverse medical challenges and improving patient care.

In this comprehensive analysis, we have delineated the landscape of clinical trials involving engineered biomaterials, revealing key trends and insights. Our study highlights the United States, Canada, and Italy as leaders in this burgeoning field, with remarkable contributions to trial conduct. These trials predominantly focus on ophthalmology, dentistry, and vascular medicine, underscoring the versatility of biomaterials across varied clinical domains. Notably, the demographic span of these trials is broad, encompassing adults and older adults

from both genders, thus reflecting the universal applicability of these materials. In terms of scale, most trials are modest in size, typically enrolling fewer than 100 participants, with a notable frequency in the 11- to 20-participant range. Nearly one-third of the trials were on medical devices, and another 10% of the trials have progressed to phase 4 of the clinical study phases. Furthermore, our analysis reveals a notable disparity in study durations, ranging from as brief as 0.5 years for silicone in contact lenses to as long as 4.5 years for cardiac stents. In terms of material composition, synthetic and natural polymers, particularly silicone and collagen, dominate the landscape, reflecting their widespread acceptance and utilization. The material properties of these biomaterials predominantly skew toward bioresorbable and bioinert characteristics. The integration of cells with these biomaterials remains a relatively unexplored frontier in these trials. Collectively, our findings provide a crucial understanding of the current state and future directions in the application of engineered biomaterials in clinical settings, offering a valuable framework for advancing this dynamic and impactful field.

LIMITATIONS

The current analysis is subject to several limitations. First, limitations arise from the scope of the database search. The search was confined to ClinicalTrials.gov, a major database, and did not extend to other clinical trial registries in different countries. Consequently, there is a possibility that additional trials may have been overlooked, rendering the search somewhat incomplete. Second, this analysis lacks validation regarding whether completed studies have been subsequently published. Only interventional trials that have reached completion or are currently active (not recruiting) were included. While this survey provides insights into the general trends in global biomaterials research, it does not substantiate these findings through scientific literature. Last, of 788 clinical trials analyzed, the majority (69%) lacked FDA-defined phases or pertained to device trials. Within this category, nearly half of the studies focused on contact lenses. Regarding the clinical study phase of other biomaterials, 70 studies (9%) were classified as phase 4 trials. This highlights a considerable gap in the clinical translation of developed biomaterials, suggesting that there is still a substantial journey ahead in this domain.

FUTURE TRENDS

As research into advanced biomaterials continues and clinical trials for these materials progress, great advances in technology are anticipated (Fig. 1). In ophthalmology, the transition to the clinic involves the development of smart contact lenses equipped with sensing capabilities to monitor intraocular pressure and other physiological parameters (69–72). The development of power-scavenging microsystems for smart contact lenses represents an eminent advancement in wearable ophthalmic devices. These smart contact lenses offer continuous monitoring of ocular parameters and facilitate early detection of eye-related conditions. In addition, the integration of safe, durable, and sustainable self-powered technology ensures reliable and long-term use of these devices without the need for external power sources. Pressure-triggered microfluidic contact lenses further enhance functionality by enabling targeted ocular drug delivery, optimizing treatment efficacy while minimizing side effects. Flexible and semitransparent silicon solar cells provide a renewable power supply to smart contact lenses, ensuring continuous operation and enhancing their utility as a seamless and self-sustaining solution for personalized eye care.

Emerging technologies in wearable electronics, including three-dimensionally printed electronic skin, graphene-based smart skins, neuromorphic sensorimotor loops, and nanoengineered ink, are revolutionizing health diagnostics (73–76). These innovations offer multifunctional capabilities such as strain, pressure, and temperature sensing, enabling high-precision monitoring and interaction with the environment. By providing real-time feedback and advanced sensorimotor capabilities, these technologies have the potential to valuably improve health care outcomes and enhance personalized patient care.

In cardiology, smart coronary stents incorporating sensors for real-time monitoring of vessel patency and drug release are advancing toward clinical implementation, offering personalized treatment strategies and reducing the risk of restenosis (77–79). Implantable multifunctional sensing platforms, including self-reporting stents and vascular electronics, represent cutting-edge solutions for cardiac monitoring. These devices integrate sensors and electronics to continuously monitor cardiac parameters such as heart rate, rhythm, and blood flow, offering real-time insights into cardiovascular health. Self-reporting stents enable early detection of in-stent restenosis and cardiac functional dynamics, while vascular electronics provide valuable data on hemodynamics within blood vessels. Together, these implantable technologies offer a comprehensive approach to diagnosing and managing cardiac conditions, potentially improving patient outcomes through timely intervention and personalized treatment strategies.

In knee osteoarthritis, nanoparticles are being developed for cartilage regeneration, offering targeted drug delivery and enhanced therapeutic efficacy to alleviate pain and improve joint function (14, 80). Nanoparticles can be engineered to encapsulate growth factors or small molecules, allowing for targeted and sustained release at the site of cartilage injury. These nanoparticles penetrate the cartilage matrix, delivering therapeutic payloads to chondrocytes and progenitor cells to stimulate proliferation and differentiation. In addition, nanoparticles can be functionalized to enhance cellular uptake and targeted delivery while also serving as carriers for imaging contrast agents to monitor cartilage regeneration in real time. Ongoing research aims to optimize the formulations and delivery methods of these biomaterials and nanoparticles to enhance their therapeutic efficacy and safety in clinical settings.

Dermatology is witnessing the emergence of skin patches equipped with advanced wound healing agents, facilitating faster wound closure and scar reduction (81–84). Polysaccharide-based transdermal patches, multifunctional microneedle patches, and transforming bio-patches into hydrogels are innovative approaches for chronic wound healing. Polysaccharide patches use materials like chitosan or alginate, delivering bioactive agents to promote healing while providing a protective barrier. Multifunctional microneedle patches painlessly penetrate the skin, delivering therapeutic compounds directly to the wound site, accelerating closure, reducing inflammation, and preventing infections. Transforming bio-patches into hydrogels support tissue regeneration, creating a moist environment conducive to healing and minimizing scar formation, ultimately improving cosmetic outcomes. These advancements hold promise for enhancing wound healing processes and improving patient outcomes in chronic wound management.

Dental applications are moving toward injectable hydrogels designed for pulp-dentin and periodontal regeneration, providing minimally invasive solutions for treating dental caries and periodontal diseases (85–87). Composed of biocompatible polymers, these hydrogels encapsulate growth factors, antimicrobial agents, or stem cells to promote tissue regeneration at the target site within the oral cavity. By providing a scaffold for cell attachment and controlled release of therapeutic agents, they facilitate the regeneration of dentin, pulp, and periodontal ligament while ensuring precise placement and adaptation to irregular tissue contours. The ongoing research is aimed at optimizing their formulation and efficacy for widespread clinical use.

Last, in oncology, cancer immunotherapy encompasses a diverse range of approaches aimed at harnessing the power of the immune system to combat cancer (88–90). Immune checkpoint inhibitors work by unleashing the immune system's ability to recognize and attack cancer cells, thereby enhancing antitumor immune responses. T cell transfer therapy involves genetically modifying a patient's own T cells to recognize and target cancer cells, offering a personalized and potent treatment option. Monoclonal antibodies target specific proteins on cancer cells, facilitating their destruction by the immune system. Treatment vaccines stimulate the immune system to recognize and eliminate cancer cells, offering a proactive approach to cancer treatment. In addition, immune system modulators regulate immune responses to enhance antitumor activity while minimizing autoimmune side effects. Together, these approaches represent a paradigm shift in cancer treatment, offering new and effective strategies to combat various types of cancer and improve patient outcomes.

Biomaterials already have several capabilities for on-demand sensing, including temperature, infection, and concentrations of various biological analytes (91). Future work in this area may improve the sensing capabilities, as well as integrating artificial intelligence to enable real-time adaptations to the biomaterial to better address the patient's condition. This may also include materials capable of self-healing to prolong the lifespan of the material. In addition, current materials used to aid regenerative medicine and repair damaged organs may experience advances that lead to the full fabrication of operational organs. The movement toward personalized medicine and patient-derived, autologous materials supports the future anticipation of such advances. Similarly, genetic engineering may find use in implantable biomaterials for modification of cells *in situ*. A multidisciplinary approach toward the development of future biomaterials is

likely to yield positive results for clinical translation and patient care. Through the development of these advanced biomaterials, an increase in composites and combinations, as well as autologous materials, is expected. Similarly, bioactive and bioresorbable materials are likely to take the forefront. As researchers continue to innovate with biomaterials, the distribution of clinical trials will change accordingly to focus on these future biomaterials and their clinical applications.

MATERIALS AND METHODS

Systematic search of database

The study aimed to conduct a comprehensive analysis of all clinical trials involving engineered biomaterials by using the ClinicalTrials.gov database. The search was executed in August 2023, and the analysis encompassed various attributes of the included studies, including the study title, URL, target disease, condition, intervention, biomaterial category, biomaterial type, specific biomaterial used, biomaterial properties, incorporation of cells, participant age and gender, clinical study phase, enrollment figures, study location, and the study's start and end dates. The corresponding data were systematically collected from the included studies and organized into dataset (dataset S1 and dataset S2).

Content analysis of clinical trials

The studies were categorized as either single-center or multicenter trials, depending on the number of locations where the research was conducted. Target diseases were classified on the basis of the specific organ or tissue under investigation, with categories including ophthalmic, blood vessel/stent, skin, bone/dental, dental, bone, reproductive, cartilage, blood vessel, lung, and others. The "others" category encompassed studies focusing on target tissues or organs such as the brain, cardiac, digestive, kidney, ligament, lung, nerve, and pancreas. The diseases of the oral cavity included both dental and bone/dental categories. For diseases of blood vessels, both blood vessel and blood vessel/stent categories were included.

The biomaterials used in these studies were further classified into categories such as polymers (both natural and synthetic), ceramics, combinations, autologous materials, metals, and composites. Composite biomaterials were defined as those resulting from the blending of two materials with distinct physical and chemical properties to enhance the base material's characteristics (e.g., dental composite restorative material). In contrast, a biomaterial was categorized as a combination when two materials were combined but not blended, typically serving a specific function, as seen in drug-eluting cardiac stents with a polymer coating on a metal surface for controlled drug release. Autologous biomaterials were derived from the same individual who acted as both the donor and recipient, including examples such as platelet-rich plasma, platelet-rich fibrin, skin grafts, and bone grafts. Biomaterials were also sorted on the basis of their properties, which included being bioresorbable, bioinert, or bioactive.

Biostatistical analysis

All data are presented in both percentages and absolute numbers. Data analyses were conducted using Microsoft Excel (Microsoft Inc., USA). Comparative analysis of individual subgroups was visually represented through pie and bar charts. Furthermore, choropleth maps, created with Microsoft Excel, were used to illustrate the geographical distribution of the included studies. Gantt charts were used to represent the study duration.

Supplementary Materials

This PDF file includes:

Legends for datasets S1 and S2

Other Supplementary Material for this manuscript includes the following:

Datasets S1 and S2

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