Transformative Advances in Biomedical Research and Clinical Practice: Navigating the Present and Envisioning the Future

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Abstract. This comprehensive review elucidates pivotal advancements in biomedical laboratory and clinical research recent years, underscoring their profound implications for healthcare innovation. We explore cutting-edge developments in genomic sequencing, bioinformatics, and CRISPR-Cas9 gene editing, which have revolutionized our approach to diagnosing and treating genetic disorders. Additionally, the review highlights key clinical breakthroughs, including seminal clinical trials introducing new medications and therapies, the rapid evolution of vaccine technology, and the strides made toward realizing the full promise of precision medicine. A critical analysis of how laboratory discoveries are being translated into clinical applications offers insights into the refinement of clinical guidelines, diagnostics, and therapeutic interventions. We also spotlight the emerging frontiers in research, such as regenerative medicine and the integration of artificial intelligence, emphasizing the indispensable role of interdisciplinary collaboration in driving future healthcare innovations. Reflecting on the cumulative impact of recent findings, we discuss the ongoing shift toward a healthcare paradigm that is increasingly personalized, effective, and forward-thinking. This review accentuates the imperative for ongoing research and cross-disciplinary partnerships to surmount complex health challenges and enhance patient outcomes.

Keywords: Biomedical Innovations; Clinical Research Breakthroughs; Genomic Sequencing Technology; CRISPR-Cas9 Applications; Precision Healthcare; Emerging Vaccine Technologies; Advanced Bioinformatics; Regenerative Medicine Frontiers; AI Integration in Medicine; Interdisciplinary Research Collaboration

1. Introduction

1.1. Brief overview of biomedical laboratory and clinical research

Biomedical laboratory and clinical research are essential pillars of modern healthcare, driving advancements in diagnosis, treatment, and our understanding of diseases. Laboratory research delves into the biological and chemical foundations of health and illness, using technologies like genomics and bioinformatics to uncover disease mechanisms. Clinical research translates these discoveries into real-world applications, through trials that evaluate the safety and efficacy of new treatments. Together, these fields work synergistically to innovate and improve patient care, leading to groundbreaking therapies and personalized medicine. Notable references include the Human Genome Project (Collins FS, et al., Nature 2003) and pivotal clinical trials like the CREDENCE study on canagliflozin (Perkovic V, et al., N Engl J Med 2019), showcasing the direct impact of research on healthcare.

1.2. Importance of these fields in advancing healthcare

The fields of biomedical laboratory and clinical research are crucial for advancing healthcare, enabling breakthroughs in understanding diseases, developing new treatments, and improving patient outcomes. Laboratory research uncovers the molecular and genetic bases of diseases, leading to the identification of new therapeutic targets. Clinical research, through rigorous trials, translates these discoveries into effective treatments and vaccines, directly impacting patient care and public health. These fields have been instrumental in advancements such as personalized medicine and targeted therapies, significantly improving survival rates and quality of life for patients with chronic conditions like cancer and cardiovascular diseases. Key references include the development of targeted cancer therapies (Sawyers CL, Nature 2004) and the impact of clinical trials on improving cardiovascular outcomes (Yusuf S, et al., Lancet 2004), illustrating the profound influence of research on healthcare evolution.

2. Recent Advancements in Biomedical Laboratory Research

Recent advancements in biomedical laboratory research, particularly in genomic sequencing technologies and bioinformatics, have revolutionized our understanding of genetic diseases.

2.1. Novel Technologies and Methodologies

Biomedical laboratory research has seen transformative advancements, especially in genomic sequencing technologies and bioinformatics, revolutionizing our comprehension of genetic disorders.

2.1.1. Genomic Sequencing Technologies

Genomic sequencing technologies, such as next-generation sequencing (NGS), have dramatically enhanced our ability to analyze genetic material quickly and cost-effectively. NGS has enabled the comprehensive mapping of genetic mutations associated with various diseases, improving diagnostic accuracy and facilitating personalized medicine. Rehm HL (2013) further underscored the critical role of disease-targeted sequencing in refining clinical diagnostics and tailoring treatment strategies, highlighting its foundational place in precision medicine. For example, the application of whole-genome sequencing has uncovered novel genetic variants implicated in rare genetic disorders, offering insights into their molecular mechanisms and identifying potential therapeutic targets. This progress has been pivotal in oncology, where genomic profiling of tumors has led to the development of targeted therapies, significantly improving patient outcomes (Robinson, D. R., et al., Nature Medicine, 2017).

2.1.2. Advances in Bioinformatics for Data Analysis

The explosion of genomic data generated by advanced sequencing technologies has necessitated parallel advances in bioinformatics. Bioinformatics tools and algorithms have been crucial for interpreting the vast amounts of data, identifying disease-associated genetic variations, and understanding their functional impact. Machine learning and artificial intelligence (AI) have become integral to bioinformatics, enhancing the ability to predict disease susceptibility, prognosis, and response to treatment based on genetic information. For instance, AI-driven bioinformatics approaches have enabled the identification of novel biomarkers for cancer prognosis and the prediction of patient response to immunotherapy, leading to more personalized and effective treatment strategies (Topol, E. J., Nature Medicine, 2019). Esteva et al. (2019) highlighted the transformative potential of deep learning in healthcare, from improving diagnostic accuracy to predicting treatment outcomes, marking a new frontier in biomedical research and personalized medicine.

Together, these advancements in genomic sequencing technologies and bioinformatics are at the forefront of biomedical laboratory research, offering unprecedented opportunities for understanding, diagnosing, and treating genetic diseases. They exemplify the transition towards more personalized, precision medicine, where treatments can be tailored to the genetic makeup of individual patients, promising more effective interventions with fewer side effects.

These technologies not only deepen our understanding of the genetic basis of diseases but also open new avenues for therapeutic development and clinical practice, underscoring their importance in the ongoing evolution of healthcare.

2.1.3. Development of CRISPR-Cas9 for gene editing and its implications

The development of CRISPR-Cas9 gene editing technology has revolutionized biomedical research with its precision, efficiency, and versatility. Discovered as a part of bacterial immune systems, CRISPR-Cas9 allows for specific genome alterations by targeting DNA sequences matching its guide RNA. This breakthrough has vast implications, including the potential to correct genetic defects, treat diseases at their genetic roots, and engineer crops for better yields. In medicine, its application ranges from correcting genetic mutations responsible for diseases like sickle cell anemia to enabling the creation of more accurate disease models for research. Despite its promise, ethical and safety concerns arise, particularly regarding germline editing and unintended off-target effects. However, ongoing research aims to refine CRISPR-Cas9's accuracy and mitigate risks. This technology's implications extend beyond medicine, affecting agriculture, bioengineering, and the fundamental understanding of genetics (Jinek M, et al., Science, 2012; Doudna JA, Charpentier E, Science, 2014), signifying a pivotal shift in genetic and biomedical research capabilities. The National Academies of Sciences, Engineering, and Medicine (2017) provide a thorough examination of the ethical, social, and governance issues surrounding human genome editing, emphasizing the need for a global consensus on ethical guidelines.

2.2. Disease Modeling Innovations

Recent advancements in biomedical laboratory research have been significantly propelled by the development of CRISPR-Cas9 gene editing technology, alongside innovations in disease modeling, including the use of organoids, 3D bioprinting, and advancements in animal models.

2.2.1. Development of CRISPR-Cas9 for Gene Editing

CRISPR-Cas9 has revolutionized the field of genetics by providing a precise, efficient, and relatively simple method for editing the DNA of organisms. This technology allows researchers to add, remove, or alter genetic material at particular locations in the genome. Its implications for biomedical research are profound, offering potential cures for genetic disorders by correcting mutations at their genomic source. A landmark study demonstrated CRISPR's potential by correcting a mutation associated with Duchenne muscular dystrophy in a mouse model, offering hope for treating genetic diseases (Tabebordbar, M., et al., Science, 2016).

2.2.2. Organoids and 3D Bioprinting

Organoids, three-dimensional cell cultures that replicate some of the complexities of an organ, have emerged as powerful tools for disease modeling and drug testing. These mini-organs provide a more physiologically relevant environment for studying human diseases and have been used to model conditions ranging from cancer to neurological disorders. Coupled with CRISPR-Cas9, organoids can be engineered to carry disease-specific mutations, enhancing their utility as models (Lancaster, M. A., & Knoblich, J. A., Science, 2014). Takebe and Wells (2019) discuss the engineered design of organoids for enhanced disease modeling and drug testing, highlighting their potential to mimic complex biological systems more accurately.

Similarly, advancements in 3D bioprinting have revolutionized our ability to fabricate tissue structures that closely replicate the microarchitecture of human organs. This innovative technology facilitates the precise placement of cells and biomaterials, culminating in the creation of functional tissues for both research and therapeutic applications. The utility of 3D bio-printed tissues extends to the study of disease mechanisms and tissue repair, heralding a new era in regenerative medicine with significant potential to impact patient care. Notably, Murphy and Atala (2014) in their seminal work, "3D Bioprinting of Tissues and Organs," published in Nature Biotechnology, highlight the technological advancements and the broad spectrum of applications for 3D bioprinting in creating complex tissue constructs, emphasizing its transformative role in regenerative medicine and biomedical research.

2.2.3. Advancements in Animal Models

CRISPR-Cas9 has also transformed the generation of animal models for disease research. Traditional methods of creating genetically modified animals were time-consuming and less precise. CRISPR has enabled the rapid generation of mouse models with specific genetic alterations, accelerating the pace of genetic research and drug development. Furthermore, this technology is not limited to mice; it has been applied to a wide range of organisms, expanding the possibilities for biomedical research (Hsu, P. D., et al., Cell, 2014).

These advancements not only deepen our understanding of the genetic basis of diseases but also open new avenues for therapeutic development and clinical practice, underscoring their importance in healthcare's ongoing evolution.

3. Breakthroughs in Clinical Research

Clinical research has seen significant breakthroughs up to December 2023, with pivotal clinical trials shaping the landscape of modern medicine, particularly in the development of new medications, vaccines, and the advancement of precision medicine.

3.1. Overview of significant clinical trials up to December 2023

Recent years have marked significant progress in clinical trials targeting the genetic and molecular foundations of diseases. A prime example of this trend is the study conducted by Adams, David, et al., focusing on the efficacy and safety of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy. Published in Amyloid in 2023, this randomized clinical trial provides critical insights into the treatment of a severe form of heart failure associated with this condition, showcasing the potential of RNAi therapeutics in addressing genetic disorders (Adams, David, et al., Amyloid, 2023, 30.1: 18-26). Further emphasizing the shift towards innovative genetic interventions, Aimo, Alberto, et al., review RNA-targeting and gene editing therapies for transthyretin amyloidosis in Nature Reviews Cardiology (2022). Their work highlights the broader implications and promise of such therapies in treating transthyretin amyloidosis, underlining the industry's commitment to tackling diseases at their genetic and molecular roots (Aimo, Alberto, et al., Nature Reviews Cardiology, 2022, 19.10: 655-667).

3.2. Impactful results from trials on new medications or therapies

The landscape of cancer therapy has been transformed by the successful trials of CAR-T cell therapies for various types of cancer, including lymphoma and leukemia. These therapies, which involve modifying a patient’s own T cells to attack cancer cells, have shown remarkable efficacy in patients who had previously run out of treatment options, marking a significant advancement in personalized cancer treatment (Neelapu SS, et al., N Engl J Med, 2017).

3.3. Advances in vaccine development, particularly for emerging diseases

The rapid development and deployment of COVID-19 vaccines marked a historic achievement in vaccine science, demonstrating the power of mRNA technology. Building on this success, mRNA technology is being explored for vaccines against other diseases, including influenza, Zika, and HIV. Pardi et al. (2018) explored the revolutionary era of mRNA vaccinology, detailing the technological advancements and challenges overcome to achieve the rapid development and success of mRNA-based vaccines. Early-stage trials have shown promising results, suggesting a broad potential impact of mRNA vaccine technology beyond the pandemic (Polack FP, et al., N Engl J Med, 2020).

3.4. Progress in precision medicine and personalized therapies

Precision medicine has seen remarkable progress, notably in clinical trials for targeted therapies that consider individual genetic backgrounds. In the realm of cystic fibrosis treatment, triple-combination therapy tailored to specific genetic mutations has significantly enhanced lung function and overall patient quality of life, as demonstrated by Heijerman HGM and colleagues in their pivotal study (N Engl J Med, 2019). In oncology, the development and application of poly (ADP-ribose) polymerase (PARP) inhibitors have been a testament to the precision medicine approach, particularly for treating BRCA-mutated breast and ovarian cancers. Konecny GE and Kristeleit RS provide an overview of the current practice and future directions of PARP inhibitors in ovarian cancer, acknowledging their therapeutic potential beyond BRCA mutations (British Journal of Cancer, 2016). Kristeleit Rebecca et al.'s phase I–II study further validates the efficacy of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors, highlighting the broader applicability of these inhibitors (Clinical Cancer Research, 2017). Similarly, Sun Ximu et al.'s meta-analysis and systematic review consolidate the efficacy and safety profile of PARP inhibitors in patients with BRCA-mutated advanced breast cancer (The Breast, 2021), while Lynce Filipa and Robson Mark discuss the clinical use of PARP inhibitors in both BRCA mutant and non-BRCA mutant breast cancer, illustrating the expanding role of these agents in cancer therapy (In: Targeting the DNA Damage Response for Cancer Therapy, Springer International Publishing, 2023).

4. Integration of Laboratory Findings into Clinical Practice

The integration of laboratory findings into clinical practice has profoundly impacted healthcare, guiding the development of clinical guidelines, diagnostics, and treatment strategies. This synergy between research and clinical application has led to significant improvements in patient care.

4.1. Laboratory Research Informing Clinical Guidelines and Treatments

One notable example is the integration of cholesterol management guidelines based on findings from genetic studies and clinical trials. Research identifying the role of LDL cholesterol in atherosclerosis has led to the development of statins, a class of drugs that significantly reduce cardiovascular risk. These findings have been incorporated into clinical guidelines, recommending statin therapy for patients with elevated cardiovascular risk (Stone NJ, et al., J Am Coll Cardiol, 2014).

4.2. Translation of Genomic Research into Diagnostic Tests

Genomic research has revolutionized diagnostics, enabling the development of tests that can predict disease risk, diagnose conditions, and guide treatment decisions. For instance, the discovery of the BRCA1 and BRCA2 genes and their link to increased breast and ovarian cancer risk has led to the development of genetic tests that help identify individuals at high risk. These tests have become an integral part of clinical practice, informing decisions about preventive measures and treatment strategies (King MC, et al., Science, 2003).

4.3. Adoption of New Biomarkers for Disease Management

The identification of biomarkers through laboratory research has significantly improved disease management. An example is the use of hemoglobin A1c (HbA1c) levels to manage diabetes. Research demonstrating the correlation between HbA1c levels and average blood glucose levels over several months has led to its widespread adoption as a diagnostic criterion and a target for therapy in diabetes management, improving patient outcomes by facilitating more precise control of blood sugar levels (American Diabetes Association, Diabetes Care, 2010).

5. Challenges and Ethical Considerations

5.1. Discussion of challenges faced in both laboratory and clinical research

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5.2. Ethical issues around genetic editing technologies and patient consent

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6. Future Directions and Conclusion

The future of biomedical research and clinical practice is poised for transformative breakthroughs, with several areas promising substantial advancements in healthcare. Precision medicine, driven by genomic research, is expected to tailor treatments more closely to individual patients' genetic profiles, improving efficacy and minimizing side effects. The burgeoning field of regenerative medicine, including stem cell therapy and tissue engineering, holds the potential to repair or replace damaged organs and tissues, offering new hope for chronic diseases and injuries (Takahashi K, Yamanaka S, Cell, 2006).

6.1. Potential future breakthroughs and areas of research that are promising

Another promising area is the integration of artificial intelligence (AI) and machine learning in diagnostics and treatment planning, which can enhance the accuracy of diagnoses and optimize treatment regimens based on vast datasets that no human could analyze alone (Topol EJ, Nat Med, 2019). Additionally, the development of novel vaccines using mRNA technology, as demonstrated during the COVID-19 pandemic, illustrates the rapid response potential against emerging infectious diseases (Polack FP, et al., N Engl J Med, 2020).

6.2. The importance of interdisciplinary collaboration in advancing health outcomes

Interdisciplinary collaboration is crucial in realizing these advancements. The convergence of biology, engineering, computer science, and data analytics has already accelerated progress in genomics, bioinformatics, and biomedical engineering. Such collaborations are essential for tackling complex health challenges, as they bring diverse expertise and perspectives to the research table, fostering innovation and speeding the translation of research findings into clinical applications.

6.3. Final thoughts on the impact of recent research on the future of healthcare

In conclusion, the impact of recent research on the future of healthcare is profound. Advances in genetic research, regenerative medicine, AI, and vaccine technology are not only paving the way for new treatments and diagnostics but also reshaping our approach to healthcare. These developments promise a future where medicine is more personalized, effective, and responsive to global health challenges. The continued integration of laboratory findings into clinical practice, supported by interdisciplinary collaboration, will be key to realizing the full potential of these advances, ultimately leading to improved health outcomes and quality of life.

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References

1. COLLINS, Francis S., et al. A vision for the future of genomics research. nature, 2003, 422(6934): 835-847.
2. PERKOVIC, Vlado, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England journal of medicine, 2019, 380(24): 2295-2306.
3. SAWYERS, Charles. Targeted cancer therapy. Nature, 2004, 432(7015): 294-297.
4. YUSUF, Sleight, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The New England journal of medicine, 2000, 342(3): 145-153.
5. REHM, Heidi L. Disease-targeted sequencing: a cornerstone in the clinic. Nature reviews genetics, 2013, 14(4): 295-300.
6. ROBINSON, Dan R., et al. Integrative clinical genomics of metastatic cancer. Nature, 2017, 548(7667): 297-303.
7. TOPOL, Eric J. High-performance medicine: the convergence of human and artificial intelligence. Nature medicine, 2019, 25(1): 44-56.
8. ESTEVA, Andre, et al. A guide to deep learning in healthcare. Nature medicine, 2019, 25(1): 24-29.
9. JINEK, Martin, et al. A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. science, 2012, 337(6096): 816-821.
10. DOUDNA, Jennifer A.; CHARPENTIER, Emmanuelle. The new frontier of genome engineering with CRISPR-Cas9. Science, 2014, 346(6213): 1258096.
11. NATIONAL ACADEMIES OF SCIENCES, et al. Human genome editing: science, ethics, and governance. National Academies Press, 2017.
12. TABEBORDBAR, Mohammadsharif, et al. In vivo gene editing in dystrophic mouse muscle and muscle stem cells. Science, 2016, 351(6271): 407-411.
13. LANCASTER, Madeline A.; KNOBLICH, Juergen A. Generation of cerebral organoids from human pluripotent stem cells. Nature protocols, 2014, 9(10): 2329-2340.
14. TAKEBE, Takanori; WELLS, James M. Organoids by design. Science, 2019, 364(6444): 956-959.

15. MURPHY, Sean V.; ATALA, Anthony. 3D bioprinting of tissues and organs. Nature biotechnology, 2014, 32(8): 773-785.
16. HSU, Patrick D.; LANDER, Eric S.; ZHANG, Feng. Development and applications of CRISPR-Cas9 for genome engineering. Cell, 2014, 157(6): 1262-1278.
17. ADAMS, David, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid, 2023, 30(1): 18-26.
18. AIMO, Alberto, et al. RNA-targeting and gene editing therapies for transthyretin amyloidosis. Nature Reviews Cardiology, 2022, 19(10): 655-667.
19. NEELAPU, Sattva S., et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New England Journal of Medicine, 2017, 377(26): 2531-2544.
20. PARDI, Norbert, et al. mRNA vaccines—a new era in vaccinology. Nature reviews Drug discovery, 2018, 17(4): 261-279.
21. POLACK, Fernando P., et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England journal of medicine, 2020, 383(27): 2603-2615.
22. HEIJERMAN, Harry GM, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. The Lancet, 2019, 394(10212): 1940-1948.
23. KONECNY, G. E.; KRISTELEIT, R. S. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. British journal of cancer, 2016, 115(10): 1157-1173.
24. KRISTELEIT, Rebecca, et al. A phase I–II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. Clinical Cancer Research, 2017, 23(15): 4095-4106.
25. SUN, Ximu, et al. Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: A meta-analysis and systematic review. The Breast, 2021, 60: 26-34.
26. LYNCE, Filipa; ROBSON, Mark. Clinical Use of PARP Inhibitors in BRCA Mutant and Non-BRCA Mutant Breast Cancer. In: Targeting the DNA Damage Response for Cancer Therapy. Cham: Springer International Publishing, 2023: 91-102.
27. STONE, Neil J., et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014, 129(25)_suppl_2: S1-S45.
28. KING, Mary-Claire; MARKS, Joan H.; MANDELL, Jessica B. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science, 2003, 302(5645): 643-646.
29. AMERICAN DIABETES ASSOCIATION. Diagnosis and classification of diabetes mellitus. Diabetes care, 2010, 33.Supplement_1: S62-S69.