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Applications and Industrialisation of Nanotechnology

Ahmed Abushomi *

Kellogg College – University of Oxford

Outline

Nanotechnology-enabled devices from diagnosis to treatment

The ability to diagnose at an early stage, reduce post-surgical complications, and provide accelerated treatment for the most unprecedented diseases at a lower cost would be an invaluable step for the future of healthcare.

Some of the current medical interventions, while rigorous, can be laborious, invasive and heavily reliant on traditional methods to assess patient status. Such procedures could introduce inaccuracies as well as increase the risk of developing adverse effects on patients. Diagnosis and assessment procedures such as those used for wound assessment, cancer diagnosis, or for immune deficiencies diseases detection could fail to define patient status accurately and at an early stage [1-4]. Other complexities that are often under looked are the chemical and environmental risk factors in hospital settings that are not easily controlled or fully understood [5-7]. Despite strong effort in infection control these risk factors cannot be fully eliminated using existing precautional procedures. Finally, most recent statistics indicate prevalence in a number of critical diseases. The increase in the number of people diagnosed with cancer, diabetes, and spread of newly discovered viruses in the past 10 years are examples to contextualise this challenge.

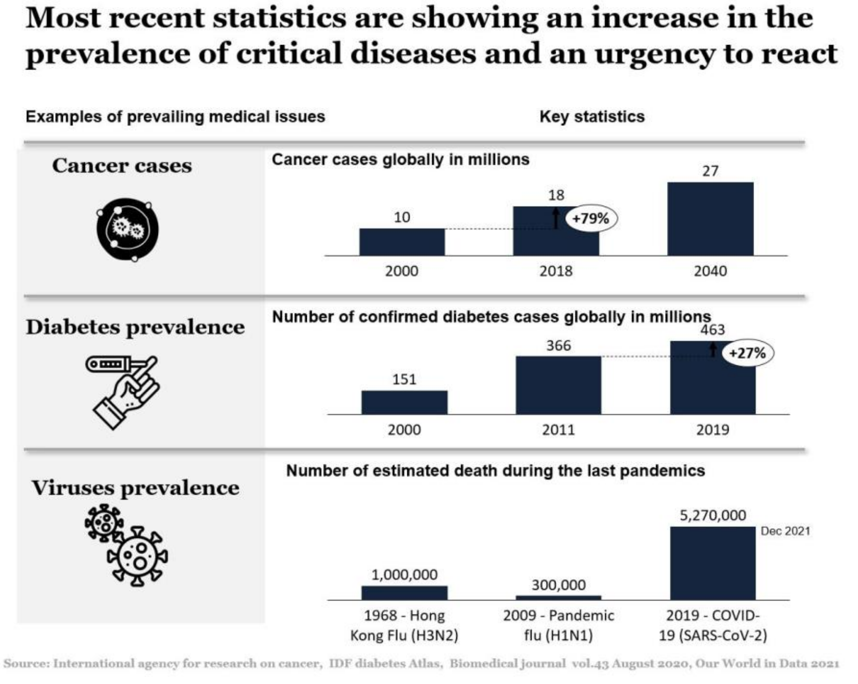


FIGURE 6.1
despite great efforts in vaccination and virus control, COVID-19 death are reaching historical numbers urging a modernisation of the current approach [112].

The increase in the number of chronic diseases cases and spread of viruses are causing a financial and operational burden on the current healthcare system. It is estimated that a typical cost associated with FDA approved cancer treatments annually can reach up to $100,000 per patient [11-12]. Furthermore, according to a published data by the American Diabetes association, the direct cost associated with diabetes patient raised by 20% since 2012 totalling a cost of $327 Billion

in the USA alone. Out of this, the study estimated that $90 Billion alone are spent due to lost in productivity [13].
Enhancing the current medical procedures and technologies will be fundamental to reduce the cost and operational complexities in healthcare. The implications of these scientific, financial, and operational complexities necessitate a modernisation of current medical interventions in order to improve patient outcome, enhance operational effectiveness in clinical setting and create the right strategy to prevent the next pandemic. It is most likely that the next world challenge will be associated with viruses, contamination and global warming. Therefore, in this chapter a value-based approach is proposed exploring the advancement of medical devices that use nanotechnology to deliver value for the healthcare system.

Nanotechnology in healthcare and medical devices

The past 10 years have exhibited a steep growth of technological innovations, specifically in the area of nanotechnology and medical devices. Analysing historical publications and patent is demonstrating growth of nanotechnology-related publications by more than ~%75. Furthermore, the number of nanotechnology published patent applications has also been lineally growing in the same duration with an average annual growth rate of 23%*.
The unique properties found in nanomaterial, created an opportunity to enhance material performance for various industries introducing novel materials with distinctive characteristics that outperform the properties found in bulk materials [15-17]. Specifically, for industrial applications the electrical, thermal and conductive properties make nanocomposite suitable for light weight, heavy duties applications; bringing significant potential saving on maintenance and performance [18-22].
However, despite these visible advantages for manufacturing applications, scaling up the properties of nanoscale materials is faced with manufacturing challenges [23]. Uniformity, purity and consistency of manufacturing are some of the most reported challenges to scaling up these properties [23-27]. Therefore, the use of nanomaterial specifically, in large-scale manufacturing has been primarily limited to nano-composite or as a clay to enhance existing bulk materials properties as scalability issue to be resolved [23,28-30].
On the other hand, zooming down at the nanoscale, most viruses, physiological changes, and cell interactions occur at the nanoscale making nanomaterials perfectly tailored for biomedical applications made it an area of interests for many researchers to introduce high performing novel materials [31-33]. Specifically, for medical devices due to the biocompatibility of nanomaterial the opportunity to create a value is higher than ever before [34-35].
Reviewing the latest critically selected publications in this field and across different disciplines reveal visible advantages of using nanotechnology in medical devices. Some of these advantages including high selectivity, sensitivity to specific biomarkers, and low power consumptions; offering enhanced performance. Furthermore, nanomaterials offer biocompatibility and flexibility of material, compared to conventional rigid micro-electronics used at the present [34-37]. These features were found to be foundational for the design of high performing medical devices that purposely designed to create value. Figure 6.2 below demonstrate selective examples on the different types, sizes, shapes and distinctive characteristics that enable nanotechnology to enhance the performance and usability of the future of medical devices in different domains.

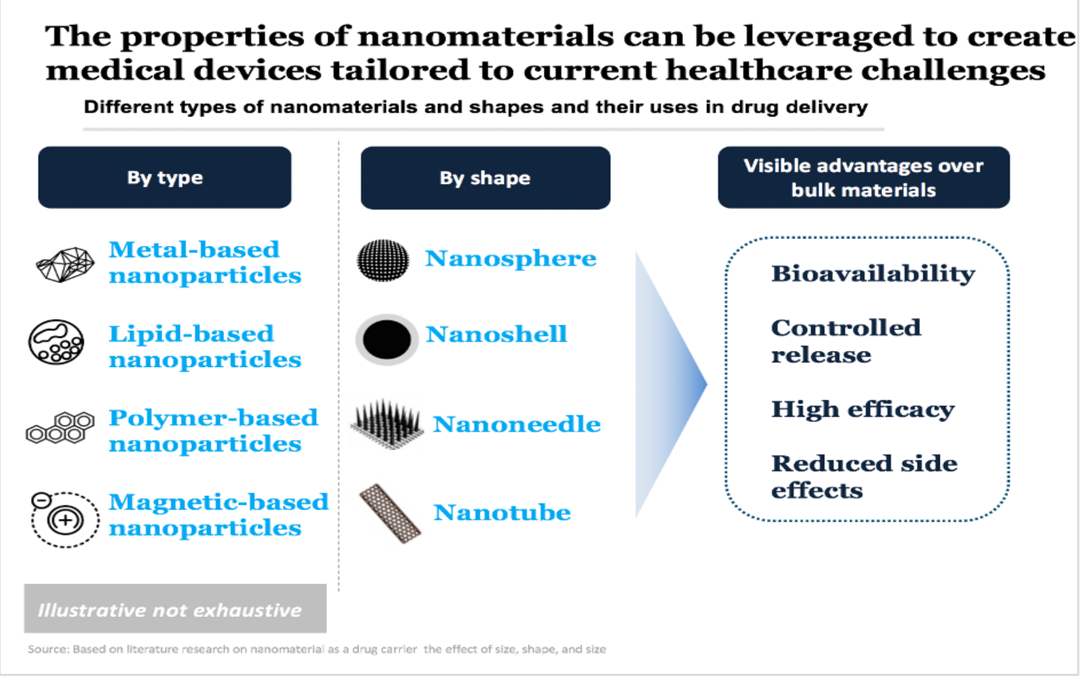


FIGURE 6.2
The high efficacy and reduced side effects of medicine are some of the advantages that can be captured using nanomaterial over bulk material.

Bioavailability, controlled drug release, high efficacy and reactivity as well the potential to reduce drugs side effects are few examples on the unique features and characteristics that can be enabled using nanomaterial in medical devices. An obvious instance, where nanomaterial can play an important role is in electronics, allowing the operation of medical devices with low voltage and high level of durability and conductivity. Another example is in wearable and integrated devices, where the unique features of nanomaterial offer flexibility capable of mimicking skin movement unlike any other material [38-40]. Conclusively with a great evidence of success, the use of nanotechnology is indeed an area worth exploring to look at the next step of healthcare operation.

Nanotechnology across the value chain

Enhancing the current medical procedures and technologies will be fundamental to reduce the cost and operational complexities in healthcare. The implications of these scientific, financial, and operational complexities necessitate a modernisation of current medical interventions to provide performance enhancement.
The previous section discussed a brief on the unique features enabled using nanotechnology that can potentially uplift the performance of conventional medical procedures and interventions. However, in order to resolve the operational, and financial complexities a value driven approach is essential in the design of a medical device. This allow the creation of a feasible solution that are directly aligned with the complications faced by health practitioners, decision makers and patients all together.

A medical product should priorities value creation, as patient outcome should remain to be the number 1 priority to assess the feasibility of using medical device in hospital setting while considering any potential risk factors. Then, other factors could weigh in such as pricing, shelf-life, versatility, and simplicity. Below are some of the additional factors to be used in order to assess the success of medical devices:

- **Financial feasibility:** One of the biggest barriers that medical devices are currently facing is its associated cost. Medical devices needs to sustain high return on invested capital relative to their cost to be successful. Providing a sharp return on investment by drastically improving operation is essential. A nanotechnology-enabled device that save 200 hours of operational cost yearly on manual and labour intensive tasks while having low associated cost (maintenance, operation, initial pricing) is what success look like [41-42]
- **Performance outcome:** The performance of a medical device should provide strong evidence of outperforming current procedures/process used. A typical example of evaluating performance include, number of hours saved, number of hospitalisation days reduced, increase in the treatment satisfaction by patients are few examples to measure performance relative to existing procedures
- **Device lifetime:** It is essential that a medical device has the longevity required to withstand daily usage, and not to be replaced regularly. Properties found in nanomaterial posses with an outstanding mechanical properties outperforming those found in bulk materials that could potentially enhance the shelf-life for medical devices
- **Risk constrains:** A set of risk measurement metric should be in place including potential toxicity, allergy on patients, and scenario evaluation in case of failure. A successful medical device development should have the right strategy to react in case of failure to obtain the highest level of safety. Later on we discuss in depth the role of nanomaterial in early-risk prevention
- **Complexity of use:** The time of medical staff is extremely valuable, in an industry where time is critical it is essential that a device does not require extensive training. Some medical devices, could require up to 300 hours of training (ref)
- **Simplicity:** Our interviews with medical practitioner revealed that the interpretations of data from medical devices is still a barrier. Simplicity of understanding the outcome and its relation to clinical cases is essential

With the above metric in mind, we envision that nanotechnology can help in the creation of more reliable and feasible solutions to add value across the entire value chain. We dissect the value chain into five segments where we see the potential of nanotechnology-enabled devices can maximize the potential value creation. These five segments are highlted in figure 6.3 below.

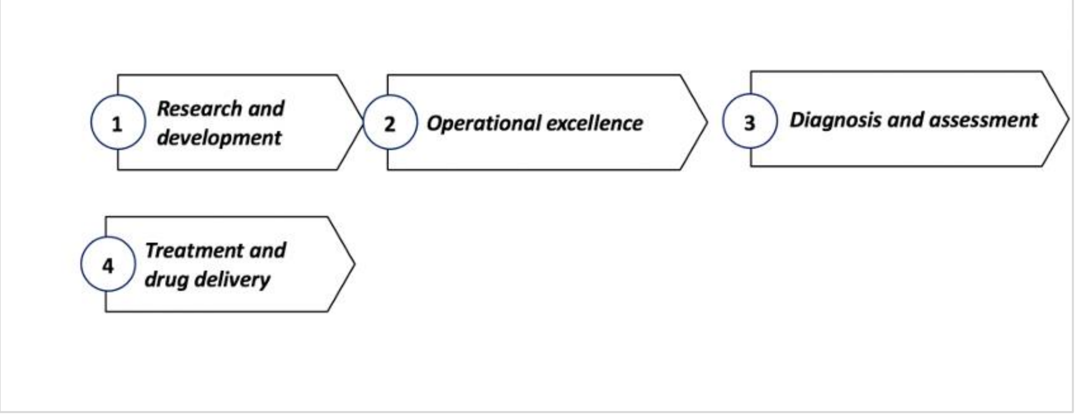


FIGURE 6.3
Capturing value using medical devices is not limited to hospital setting but start as early as at the R&D stage in the value chain.

Consequently, a design that lack a value driven approach if reached to the market space, will still lack the practicality, and ease to be used for every day's hospital operation. The market of these devices that lack a value-centric approach in our experience is seen to be very limited.
In conclusion, The future of medical devices is envisioned to make healthcare operation, easier, more productive, and focused on delivering optimal patient's outcome. However, this vision could not be realised unless the financial feasibility, regulatory considerations, and patient outcome to be incorporated at an early stage of the design. In order to measure value a tangible approach is needed to quantify the impact. This section highlighted the use of some of the quantifying metrics which will create visibility for patients and operators to capture the impact of technologies being used. The latest innovative approach including AI, data science will also create a complimentary role in reducing ambiguity of operation and create a data-driven approach for decision making. While leveraging the latest features and advances in technology is important, yet a focus on value creation should be the optimum goal at the earliest stage of designing a medical device that embed the use of nanotechnology.

Nanotechnology medical devices in R&D

Crystalizing a robust scientific understanding of our everyday occurring disease is the foundation of clinical assessment, treatment, and drug design. However, the process of innovation to transform a medical solution to commercialization can take years of extensive research. Specifically, in healthcare a clinical trial for vaccine/ drug development can take up to 20 years, a long-term process that is indeed needed to ensure safety and effectiveness. Figure 6.4 below illustrates the typical time investment in R&D from understanding to commercialization using selective vaccine examples and estimated drug development timeline per phase.

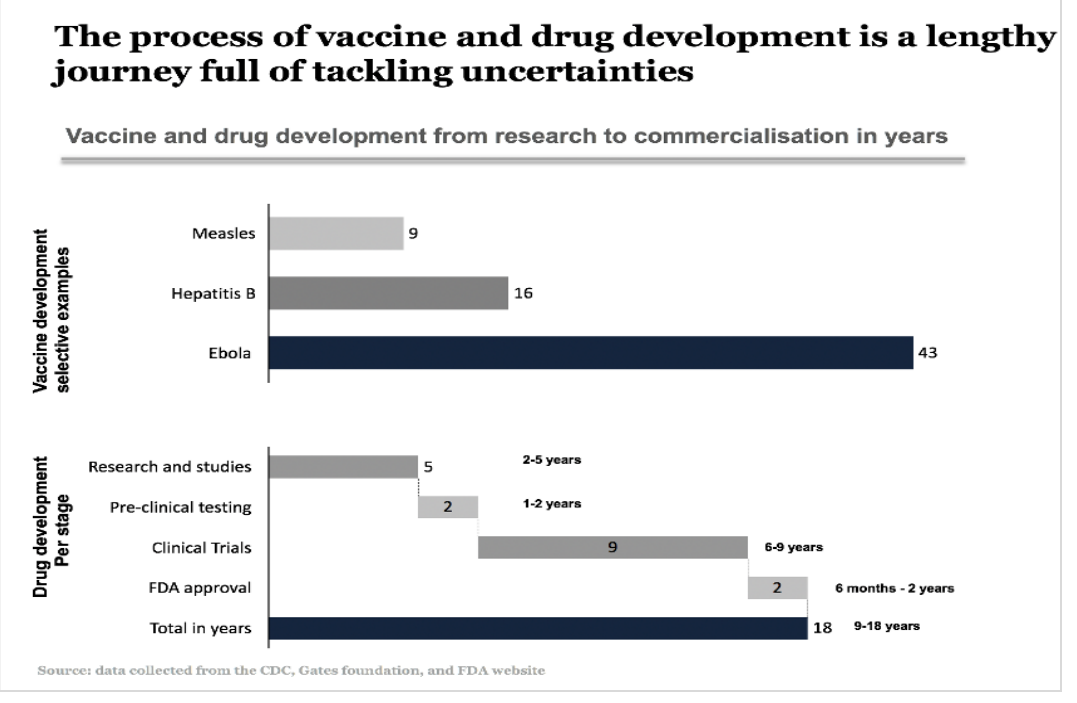


FIGURE 6.4
CDC and FDA data show that process of drug and vaccine development takes from 9 years up to 43 years for developing vaccine for Ebola. The regulatory updates and advancement in technology has accelerated this development during the pandemic.

Latest innovations in nanotechnology devices are able to contribute to the acceleration of this journey in two streams. Firstly, to help understand common uncertainties in healthcare by looking at physiological changes, phenomena and viruses at the nanoscale. Secondly, by introducing new technologies that use nanotechnology capabilities to accelerate research operation or reduce cost.

Nanotechnology medical devices answering uncertainties:

Advanced and analytical methods used in R&D environment plays an instrumental role in the discovery journey and answering uncertainties of our most unknown phenomena. Retrochiasmal disorders, and Idiopathic Pulmonary Fibrosis are two examples of Idiopathic diseases where advances in analytical tools could play a fundamental role in the discovery journey [44-45].

Nanotechnology-enabled devices unique materials are offering enhancement of these expletory tools. Absorbance measurement is widely used in biomedical application to detect and quantify molecules in a solution and is widely used in clinical research and drug discovery [46-47] . Coiled optical Nanofiber for Optofluidic was shown a potential to improve the performance of Absorbance detection by introducing high sensitivity, robustness, and low power consumption compared to standard optical systems [48].

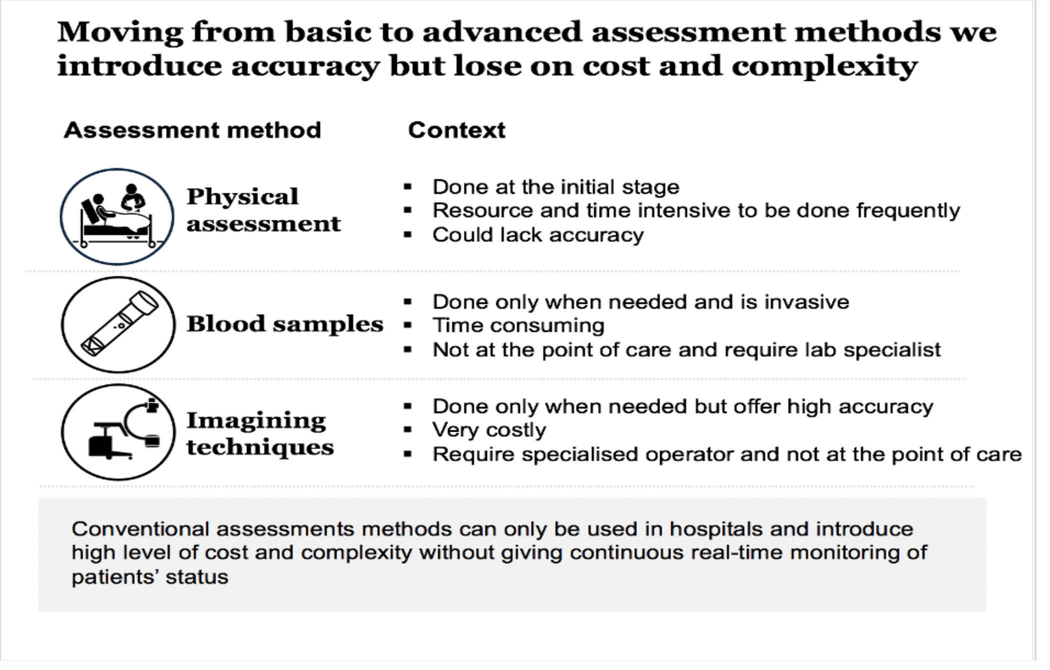
In genetic studies, Nanofluidic channels and nanomaterial enabled devices are extensively used to explore DNA interaction and regulate physiological and chemical processes [49-51]. An example of this, is a published study that uses a nanofluidic device for real-time visualization of DNA-protein interactions. Visualisation of DNA-protein interaction can be important in understanding the physiological mechanism of our body and help in the design of diagnostic and therapeutic solutions [49]. In order to study molecular interaction basic dye and labelling methods are often used. Conventional protein labelling for instance could be costly and posses with a level of complexity [52,53]. A more advanced approach to study molecular interactions is through advanced analytical tools such as atomic force microscope and imagining techniques to study DNA-binding proteins [54,55]. A combination of these advanced approach could acquire accurate results for clinical studies. However, these devices are often bottlenecked by their associated cost, and technical requirements. Further to that, does not offer the ability of continuous monitoring. The nanotechnology approach could provide an opportunity to overcome these challenging, bringing a label-free cost-effective approach for laboratory studies.

With the ability of detection at the nanoscale, nanotechnology devices are enabling to enhance our understanding of physiological interactions at a scale that could not be otherwise possible. Topographical studies, material behaviours studies, and virus's mutation studies are further examples where these devices can contribute to the knowledge base and operation of the R&D journey. This was a brief representation using examples on the potential of nanotechnology devices answering uncertainties for clinical research.

Operational excellence enabled by nanotechnology

Conventional methods to monitor efficacy of treatment or physiological changes require regular and frequent testing. Such frequent and regular testing are both cost and labor intensive. Furthermore, the evaluation metric of conventional assessment methods could lack accuracy and data are often collected manually; making it difficult to monitor the potential of long-term side effects. Advanced technologies are used as a mean to overcome these inaccuracies. Some medical devices offer a great ability to acquire accurate measurement and data on patient's status. Others also offer the ability to trigger a drug delivery mechanism when needed. However, these technologies due to its cost of operation are only used on a need basis. Further to its cost, these technologies used in hospital setting are often bulky and only suitable to be used in a hospital setting. Figure 6.5 highlights current assessment methods and their uses.

Advances in Nanotechnology offer flexible and durable material suitable to be used for wearable devices. Coupled with high sensitivity and selectivity of relevant biomarkers these devices offer - an outstanding alternative for real-time monitoring at a lower cost. Especially for chronic conditions where regular monitoring is required, the benefit of using wearable medical devices become more essential. For instance, in a study to monitor glucose for diabetic patients, wearable medical devices are benefited by the use of nanomaterial enable an accurate and stable detection of pH and glucose level from minimal sweat on skin, especially during exercise [56,57]. Other studies and potential products also highlight the role that nanotechnology play in wearable devices for diabetes [58-60]. According to recent statistics from the World health organization diabetes was the cause of more than 1.5 million deaths [61,62]. Nanotechnology is having the potential to provide continuous real-time monitoring of glucose status for patients with diabetes without the invasiveness of traditional blood meters currently used. This provides a better safety, and usability for health monitoring.



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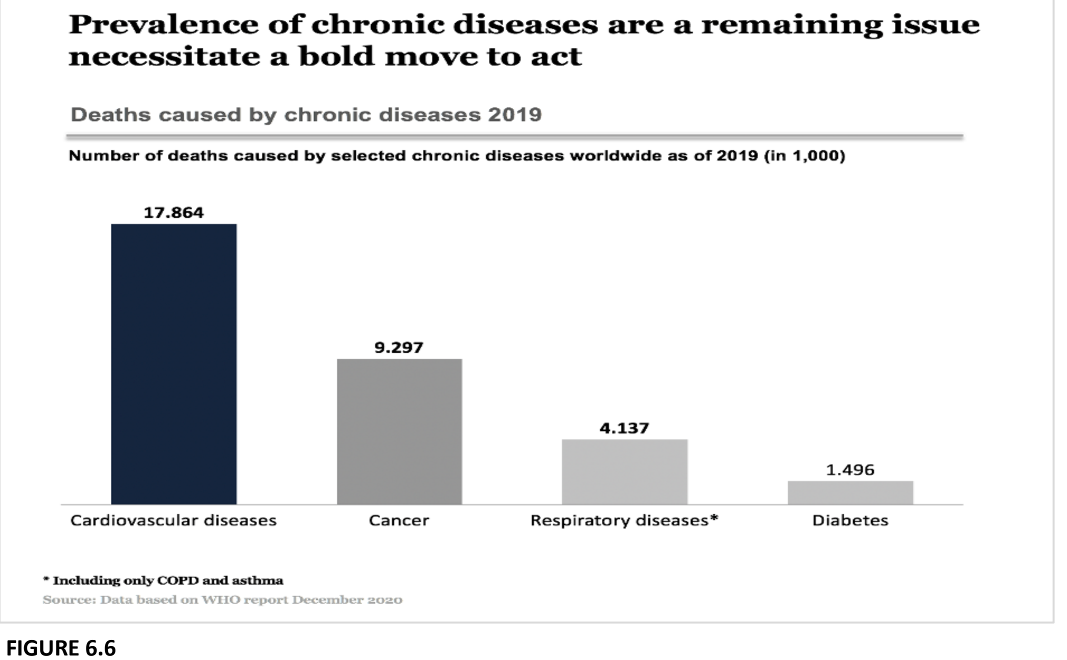

FIGURE 6.6
Recent statistics on the death caused by chronic diseases showing alarming indicators. Nanotechnology advanced properties could be a solution.

Another obvious instance, where medical device plays an important role in boosting the operational performance is seen in wound assessment. Traditional wound assessment procedures relied on visual assessment and could lack accuracy [63,64]. A further enhancement to the assessment process is through the use of nanotechnology wearable devices enabling accurate measurement of wound sites and its psychological changes, and autonomously providing time-saving opportunity. The examples covered here provide an insight on the importance of these nanotechnology-enabled devices in improving healthcare operation, specifically for chronic diseases. In a fast-moving world, with the prevalence of many diseases, and virus the acceleration of the innovation process is needed without jeopardizing on the quality of existing procedures. Figure 6.6 provides key statistics on current chronic disease prevalence, creating a necessity to act.

Advanced diagnosis at the nanoscale

A recent study published by the National Institutes of Health indicated that more than 17 million American had “undiagnosed” covid-19 cases. Around the world, scaling up this number is ought to be much higher. Further studies also uncover potential inaccuracies for some of conventional assessment and diagnosis tools used for COVID-19 [66-69]. The issue highlighted here is not explicit to COVID-19 diagnosis but extend to cover a lot of diagnosis solutions available for healthcare practitioners today.

The COVID-19 pandemic has clearly revealed the downfall of diagnosis solutions currently used. In order to improve patient’s outcome and increase effectiveness of treatment and prevention of diseases improving in current diagnosis solutions is needed. This improvement will be driven by increasing the accuracy, speed, and specificity to tackle current biases during the assessment and diagnosis phase. The speed for instance will allow fast testing for majority of population at fast base, before high risk factors occur. The accuracy is also essential to ensure patient safety and realize potential risk at early stage. Finally, most assessment and diagnosis tools used follow a “one-fit all approach”. However, with genetic, gender, and historical variabilities between patients, the future of diagnosis solutions should be more personalized. The main principle for effective treatment relies on robust diagnosis that can draw the roadmap for the treatment plan, especially for critical diseases where early diagnosis is critical in mitigating risk. Cancer, HIV, and dementia diagnosis are three examples that present the importance of early diagnosis in risk prevention [70-74]. Consequently, diagnosis solutions should act as tools to prevent risks before it occurs. This will help not only from a treatment perspective, but also to prevent the risk of the next pandemic.

Various studies address and confirm these complications and propose the nanotechnology approach as a future step to improve healthcare diagnosis [75-78]. A recent article published by Imperial College London also highlight how nanotechnology could have prevented the next pandemic [79]. The nanotechnology approach is envisioned to transform current diagnosis solutions in three ways. Firstly, to allow rapid-diagnosis solutions. Secondly, to improve accuracy of current diagnosis methods and reduce diagnosis errors. Finally, to create preventive measures towards potential diseases, infections and complications in a hospital setting.

A rapid diagnosis tool:

A typical daily journey start by conducting a physical assessment. This assessment could be followed by sample taking; a trip to the sample collection counter, which will be followed by a trip to the central lab, categorization and a work by the lab technician and roughly up to 2 hours wait to get the results. This journey is a daily routine that contextualize the cost and time taken in most healthcare institutes where diagnosis is to be conducted. In an industry where time is money, the nanotechnology approach could offer a substitution to this time-consuming process and aid decision making. Looking again at the COVID-19 cases, conventional swab or blood sample methods are invasive and require further lab testing before results are accurately obtained [80-81]. On the other hand, recent studies proposed various methods that accelerate this journey. A nanophotonic label-free biosensor, plasmonic and photothermal nano-technology biosensors are examples of some of the nanotechnology advancement highlighted in literature that could offer rapid-diagnostic solutions at the point of care [82-84]. Table 6.1 below, provides a comparative assessment of the nanotechnology approach envisioned in comparison of conventional diagnosis methods used.

TABLE 6.1
Comparative assessment between blood samples diagnosis methods and the envisioned nanotechnology approach.

Conventional approach	Future Nanotechnology approach
Takes up to 2 hours	Rapid diagnosis at the point of care
Require nurses, lab technicians, and a doctor	Could be done by nurses
Data are acquired manually	Data could be acquired digitally and be integrated into the healthcare system
Data can only be interpreted by specialists	Simplified data that facilitate decision making

Specificity and selectivity at the nanoscale:

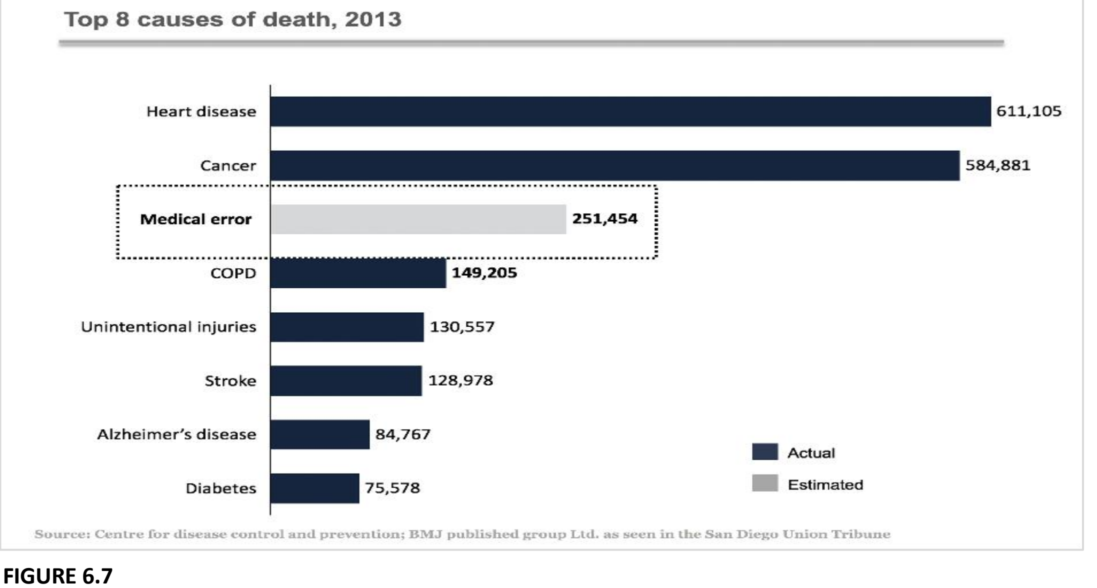

FIGURE 6.7
A famous figure published by the San Diego Tribune, highlighted the issue of medical errors being the 3rd leading cause of death in the US. Up to date, the issue of medical errors still of existence according to NCBI, 2021 [108].

In the evaluation of diagnosis methods, we often hear of diagnostic errors. Diagnostic errors have been a real concern for decades, especially in diseases where early detection of risk is not always possible [85-87]. Furthermore, specificity and selectivity are often addressed when evaluating the effectiveness of a diagnosis method. These two metrics are important to accurately the determine the absence or existing of a disease. An optimal medical diagnosis method will ideally have the highest level of accuracy in both metrics. Figure 6.7 above highlight key statistics on the diagnosis errors and its wider impact [88-89].

The difference in physiological environments and the lack of advancement in some areas in medicine could lead to such challenge in diagnosis. While many of these diagnosis errors occur due to the complexity of a certain diseases or due to our lack of understanding of some of chronic diseases [90,91], many diagnostic errors are actually preventable. In fact, recent published studies revealed that more than 20% of diagnostic errors are preventable [92-94]. The consequences of these diagnostics error could be a leading cause to complication, and potentially developing of chronic, and long-term disability.

The ability to conduct diagnosis at the nanoscale, does not only provide higher sensitivity and selectivity, but also is provide a diagnosis ability tailored to the size of relevant biomolecules. various studies highlight these limitations found in traditional cancer diagnosis and the capability of nanotechnology to improve selectivity and sensitivity targeting of cancer cells [95-97]. A self-powered device that can selectivity target human acute lymphoblastic leukemia cells in a complex environment is an example of this capability empowered by nanomaterial to enhance selectivity and sensitivity of current diagnosis methods. There are various other examples where the necessity to identity a sign of disease at a biomarker level is essential. However, the cancer diagnosis case provides an infamous example on the importance of selectivity, sensitivity and diagnosis at early stage.

A tool for effective prevention strategy:

The COVID-19 pandemic has indeed proven the importance of taking preventive measures, and the role that these safety measures play in reducing potential risks. In a hospital setting there are various environmental changes that could increase the potential of infection, virus spread resulting in the possibility of health complications. However, many of these environmental changes happen at the nanoscale, and cannot be easily controlled or mitigated. The nanotechnology approach could offer an unparallel capability to detect environmental risk at the nanoscale and prevent complications before its occurrence. Post-surgical complications due to environmental changes is a big example on this risk. Many references cover the implication of nano-enabled devices in environmental control, but very few explore the possibility of preventing infection at an early stage [99,100].

Ultimately acquiring accurate patient data, and informing definitive decisions are foundational point for early diagnostic solutions. Advanced nanotechnology devices are offering this capability to modernize current procedures. However, future diagnosis solution should also bring a preventive measure to detect risk before its potential impact enhancing current infection control strategies.

Nanotechnology tackling therapeutic complexity

Viruses mutation, spread of diseases, and antibiotic resistance are some of the addressable challenges found in modern medicine. The capability of nanotechnology in treatment and drug delivery ranges from loading drugs then releasing it at controlled level and as well targeting foreign objects; creating scavenging effects at a precision that has never been seen before. Embedding these nanoparticles properties into medical treatment can increase the efficacy of therapeutic solutions and reduce potential side effects [101-104]. Nanotechnology is offering multifunctional platform for both diagnosis and drug delivery where an instant drug delivery mechanism can be released [105]. This allow an autonomy to respond to cases where time is critical to ensure patients safety. A nanotechnology device that offers a replacement to traditional wound treatment and provide a better integration and healing of skin, is an example of therapeutics enabled by nanotechnology.

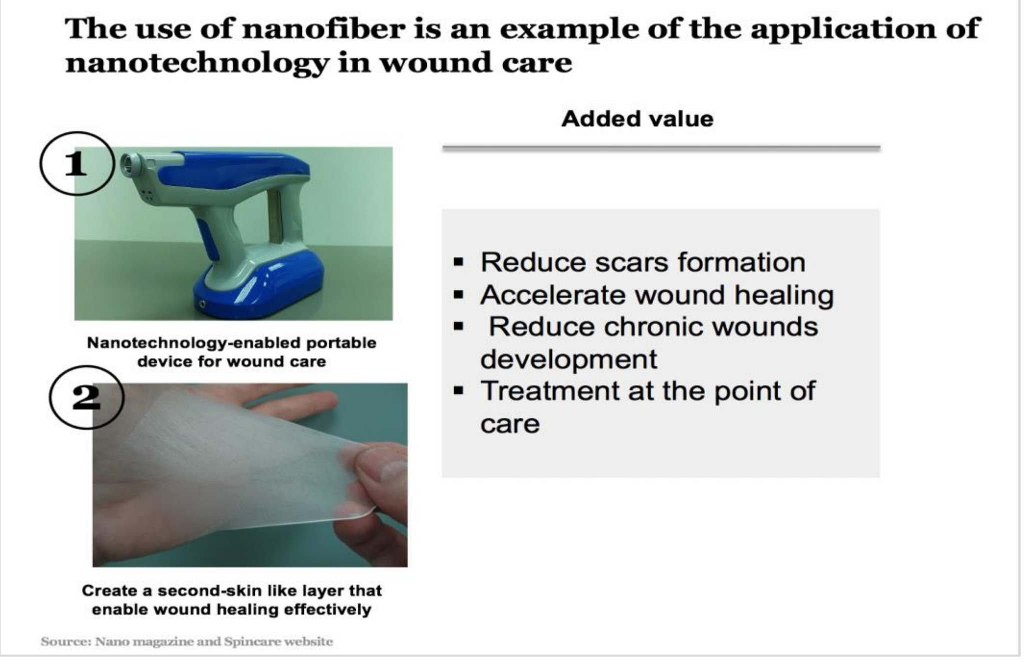

FIGURE 6.8
An example of the visible impact seen using nanotechnology-enabled devices is within wound care. The capability of portable devices enable treatment at the point of care, while reducing scars often formed using conventional treatment approach [106,107].

Another visible application of using nanotechnology devices is to be integrated in implant. An ability that enables continuous monitoring of physiological changes and accordingly trigger a drug delivery mechanism instantly and once its needed. Such envisioned capability of nanotechnology can create a visible impact, especially for chronic illness. Example of this, a device that can help trigger insulin once it is needed for diabetic patients could be a possibility in the future that is supported by wide range of recent literature [109-111].

Reimagining conventional procedures through nanotechnology

The future of nanotechnology will better our understanding in medicine and widen the knowledge gap by bringing a capability unique to biomedical applications. Nano-medical devices will have

larger involvement in accelerating R&D journey from theories to practice. Accelerating the R&D journey will help bringing more innovations and products to the market, but as well reduce cost and scalability for various applications.
Transitioning to the hospital setting, the nanotechnology approach is envisioned to increase operational efficiency. A labor-intensive process that takes few trips to the lab, another trip to the equipment room and 4 visits per day to patient’s room will be streamlined. The capability of continuous monitoring is one example given in this chapter, that will enable all-time visibility of patient’s status changes. For elderly patients with chronic diseases, this capability could be a possibility from home; resolving the capacity issue seen in many hospitals and allow connectivity between patients and doctors at the comfort of their home.
The benefit of nanotechnology extends to offer diagnosis and treatment solutions capable of identifying risk at biomarkers level rapidly, and at an early stage. Portable and integrated devices are seen to have better performance and accuracy potentially replacing bulky analytical techniques used in labs for diagnosis. In order to realize this vision, regulatory considerations will need to be updated to adapt to advancement in these technologies. Furthermore, a successful innovation in nanotechnology is most likely to occur following a multidisciplinary approach. The multidisciplinary approach will allow an effective collaboration between stakeholders, scientists, and patients to design a feasible product tailored the critical pain points in healthcare.
The global pandemics are working as a stimulant for the development of new nanotechnology-based products now more than ever before. This started to provide clear example on the benefits of these new technologies to tackle the upcoming global healthcare issues. As these technologies mature and reach an optimal level of cost of manufacturing and reproducibility the value that can be enabled will be transformative towards making a real impact.
An obvious instance, where medical device plays an important role in boosting the operational performance is seen in wound assessment. Conventional wound assessment procedures relied on visual assessment and could lack accuracy. A further enhancement to the assessment process is through the use of software technology enabling accurate measurement of wound sites and its psychological changes, and autonomously providing time-saving opportunity. Another traditional examples that highlight the role of medical devices is through the use of non-invasive cancer treatment technology that enable treatment while reducing potential side effects that may be caused due to traditional treatment methods historically used. Various studies also highlight the importance of these nanotechnology-enabled devices for accelerating the treatment of chronic diseases.

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