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Precision Pain Medicine: A Multifaceted Perspective

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Abstract

Objective: Precision medicine has become a hyped topic since most of the attention is on the diverse nature of each individual which results in different responses to the same medicine.

Literature review: We have reviewed different factors from socio-economical to genetic and epigenetic factors and how they potentially impact the person's body to react. We have reviewed over 100 studies on probable contributed factors of personalized medicine. And also we have provided guideline and solutions to achieve our goal of Precision Pain Medicine (PPM). Studies show epigenetic factors such as stress, alcohol consumption, depression, and have an eminent role. Stress can affect pain threshold, changes in loco-motor activity, body temperature and catalepsy. Having qualified devices, medication, physician perspective, genetics and even age are influential as well. A road-map has been provided as well to form a global network of PPM.

Conclusion: Our study showed that besides genetics, epigenetic, cultural and political and also plays an important role in PPM. There are many obstacles in the way as well; one of the most prominent setbacks in the progression of PPM is political issues. We have yet a long way to fill blind spots to complete our knowledge.

Keywords: Precision medicine; Personalized medicine; Epigenetic aspect; Genetic aspect; Socio-political aspect

Introduction

Every day, millions of people who suffer from different kinds of pain, take medications that do not help them. Neuropathic pain, cancer-related pain, and non-malignant pain are examples of some of the challenging conditions for pain specialists, insurance and government. This is because different patients respond differently to pain medication since the experience of pain [1-3]. Regardless of the cause of the pain, one of the reasons for this challenge is the different responses of people to painkillers. These could be due to biological, anatomical and physiological individuality as well as social and cultural difference and many other factors including sex, age, body weight, renal or hepatic function that can alter drug responses [4].

The problem has been that nature thrives on diversity. Our anatomy and physiology are as diverse as our fingerprints. It is this diversity that makes much of criminology possible. So, medicine is personal. Medicine only becomes impersonal when it becomes a matter of business or governance. Therefore, in an ideal society, the phrase personalised medicine would be considered tautologous.

Focusing on the treatment of pain, studies have shown that the quest to develop a panaceum for relieving chronic pain has consistently led to costly disappointment. Since the discovery of the Polymerase Chain Reaction (PCR) in the late 20th century and the advent of the human genome project, medicine has been able to move towards genuinely celebrating our diversity [5-7]. This has become possible because we are now able to easily map our individual differences at the genetic level. This is of course a technological breakthrough and established models of business and governance have traditionally been slow to adapt to technology.

This article is about roadmaps in which scientists and health professionals may be able to help to improvement pain relief in different society. We believe that looking at intervening and effective factors in precision pain treatment can help achieve this goal. Therefore, in the first step, we reviewed what we know to find, what we do not know, and secondly desige a roadmap to reach it. Ultimately, our goal is to do our part in breaking down barriers between policy-makers and those affected by such policies which, ironically, include the policy-makers themselves.

Different Aspects Effective in PPM

Environment perspective

Epigenetic aspect: Two factors affect whether or not you and I become ill; our genes and our environment [8]. The same two factors affect whether or not our bodies respond to a particular medication. That sounds deceptively simple. However, we cannot design treatment regimen on the basis of either genes or the environment because our response to treatment depends on the interaction between the two [9-11]. This means that the presence or absence of a gene is not enough for us to conclude that a treatment regimen will be effective; the environment must also be taken into consideration. Similarly, understanding the environmental and socioeconomic factors that affect a patient is also not enough to ensure that a proposed treatment regimen is likely to be effective.

Epigenetics refers to the inheritable or heritable environmental phenomenon, effective to gene regulation that caused by alteration in a chromosome, without change in DNA sequence [8,12]. Epigenetic main machinery includes DNA methylation, histone modifications, and noncoding RNAs [13]. Epigenetic changes that occur due to the depression, stress; nerve injury and consumption of substances such as alcohol directly and indirectly affect pain and the drug's effects [12,14-16]. There is a recurring cycle between pain, depression and epigenetic changes.

Depression is common in developing countries, especially in women, with a vicious cycle of poverty, depression, and disability [17]. DNA methylation modifications occur in the depression. In this regard, Brain-Derived Neurotrophic Factor (BDNF) hyper methylations to be associated with MDD or depression in general [18]. After depression or event lead to it, chromatin remodeling of BDNF promoters cause to site-specific increased BDNF transcription, that mediate some behavior exposure to stress in humans and animals. Increase of BDNF in serum and intra cortical effects on the primary motor cortex and also, associated with increased sensitivity to heat pain (heat hyperalgesia) and reduction of pain inhibition during noxious stimulation(mechanical hyperalgesia) [19,20]. On the other hand, long-term neuropathic pain causes depression and increase in BDNF protein expression. Also, nerve injury caused histone acetylation at the promoter regions of BDNF [21]. Consequently, in spinal cord up-regulates the expression of BDNF may contribute to the induction or maintenance of neuropathic pain [22].

It also have been reported epigenetic changes occurs in acute pain. We know that after acute pain induction, changes in the histone acetylation, increase Histone Deacetylase (HDAC) expression. Therefore, It is believed HDAC inhibitors can be effective in inflammatory pain relive [23,24].

Working stress, stress due to social pressures and natural disasters are the main hazard stressors in developing countries [25-27]. Stress is one of the well-known causes that induce epigenetic changes. The behavioral responses to the stress include increase in pain threshold, changes in loco-motor activity, body temperature and catalepsy [28].

Environmental stressors, such as childhood problems, social complications, interpersonal conflicts and trauma, have been recognized to contribute to the development and progression of mental disorders, including major depressive disorder [18,29]. It has been supposed that epigenetic changes are one of main mechanisms which lead to the development of depressive symptoms. Stress-associated epigenetic changes in several genes were correlated with depression such as BDNF. Epigenetic changes in glucocorticoid signaling, serotonergic signaling and neurotrophin genes appear to be the most promising therapeutic targets for future research's [29]. Stress also could affect the pain threshold. Stress modulates pain perception in two different ranges. It means stress can result in either induced analgesia or hyperalgesia [28]. Therefore, the need for analgesia and its response will also vary.

Alcohol consumption could also make a difference in responding to painkillers with epigenetic changes and these should be considered when administering the drug. Alcohol exposure alters factors that modify gene expression in both animals and humans [30]. According to the reports, the epigenetic changes caused by chronic alcohol exposure or consumption are similar to changes occur after chronic pain such as increase in methylation and HDAC activity [31,32]. It can be concluded that epigenetic modification due to environmental exposure affects the severity and durability of pain as well as the expression of pain attribute proteins [31,32]. Knowing the epigenetic factors in each society seems necessary for prescribe analgesics and control the response.

Nutritinal aspect: One of the most important factors in designing personalized pain medicine in a community knows the diet of individuals. Because, maybe one of the notable is the relationship between pain severity and food. On the other hand, we need to know we have not only drug-drug interaction, but also drug-food, beverage, and dietary supplements as well. These interactions often result in mal-absorption of the medicine which has been taken.

This interaction can be discussed about on both absorption state and epigenetic state. The people in health care system know before one or more NSAIDs or any other kind of analgesics has been prescribed for a patient, the doctors have asked about their diet beforehand. This is an important aspect. According to a study, acetaminophen should be taken with an empty stomach and if the stomach is not empty, especially if a food containing pectin has been eaten, the onset of its function delays on the other hand, NSAIDs should be taken with a full stomach [33]. These are only a small amount of knowledge we need to know in order to take the right medication.

Very little attention has been paid to this fact that, food we have taken for years have made what we are now and how we feel. Diet plays an important role in our lives, from looking good to feeling good. Having a balanced diet help us live a longer and more productive life. It also affects how our body response to different stimuli including pain. in order to see how diet can affect our perception of pain, we need to know both its epigenetic impacts and its interactions with the taken medication.

Epigenetic can affect DNA methylation, acetylation and methylation of histones, and noncoding RNA expression. Acetylation and de-acetylation of histone is related to changes of lysine residue within N-terminal tail which can be caused by Histone Acetyltransferase "HAT" or Histone Deacetylate Deacetylases "HDAC" [32,34]. Histone acetylation makes the nucleosome less condensed thus transcriptions becomes easier [32,34]. Studies have shown HDAC inhibitors can relieve inflammatory pain. Several studies have also shown that HDAC inhibitors can have anti-nociceptive effects on neuropathic pain. Interestingly other studies have shown the HAT inhibitors role in anti-nociceptive affect in neuropathic pain. Histone methylation is another epigenetically factor in pain perception. Histone methylation can both repress and activate gene transcription depending on the location and content which goes through methylation [32,34]. Unlike histone acetylation which is contributed to chronic pain, it is unclear whether histone methylation also has the same function or not [32,34]. DNA methylation is referred to the action of adding methyl group to the fifth carbon of cytosine residue located next to guanine residue "CpG sites". Area of DNA with high aggregation of CpG sites can be found mostly at the start of gene sequence within the promoter area. DNA methylation directly affects gene transcription. Both peripheral inflammation and peripheral nerve injury can enhance global DNA methylation. So if we block DNA methyl transferase we can also block both inflammatory pain and neuropathic pain [32].

Understanding these processes is vital in order to study the dietary effects on pain perception. Methyl donor diets help DNA methylation by one-carbon pathway. Foods containing choline, folate, methionine, riboflavin, pyridoxine, and cobalamin are in this group. High intake of green vegetables and folate was associated with lower DNA methylation, expressed as less than two genes methylated [35].

Supplementation with folic acid alone or in combination with Vitamin B12 resulted in an increase in global DNA methylation [36]. Anti-nociceptive substances can be found in polyamines such as spermidine, supermini, and putrescine which can be found in legumes such as soybeans, cereals, and mushrooms [37-40]. They are endogenous regulators of specialized calcium-sodium channels such as TRPV1, glutamatergic receptors [37]. At the end, we need to conclude the relationship between epigenetic aspect of diet and precision medicine. As mentioned there is evidence proving the relationship between epigenetics and medication, and foods?

Long term using omega-3 can provide a vast range of prostaglandins, which play role in peripheral anti-inflammatory mechanisms. The majority of pain syndromes are aroused by inflammation; therefore, omega-3 has a notable role in decreasing pain [37-41]. In case of inflammatory pain flavonoids, can be of great importance [37,42,43]. Flavonoid also plays important role in neurogenic pain. It can reduce hyperalgesia. In case of general pain, curcumin is an important bioactive [37,44,45]. It can be found in turmeric. Most of the nutrients mentioned above contain poly phenol which can signify the importance of it in pain perception [37].

American diet is known as somehow proinflammatory diet. The reason to use this word for American diet is because it mostly lacks vegetables, fruits, antioxidants, phytochemical, and omega-3 fatty acid which can promote the development of the proinflammatory state [46]. On the other hand Mediterranean diet has shown promising results on reduction of pain and inflammation, it can be due to higher vitamin E, secoiridoids that can be found in olive oil, that can be found in it, and the most important aspect of it is the MUFA-Monounsaturated fats consumption [47,48].

From genetically view, there are evidence explaining the genetic diversity and the variability in a patients response to an analgesic treatment, however we know usually patients are given different kinds of analgesics in order to cover each other up. This matter tells us about the complexity of the processes which medications go through. We also know that foods can affect drugs absorption so this might show the importance of dietary aspect of drug absorption but not its epigenetic interactions [49].

Now that we grasp the whole idea of dietary epigenetic impact on pain, we need to understand its interactions with pain killers and other medication in order to reach our goal, precisioning pain medicine.

Low energy foods can result in more severe pain. A study which had took place in different hospitals, have demonstrated the importance of balanced nutrition with a proper amount of calory in pain perception. The difference is significant enough to be mentioned [50].

Evidence showed ethnic differences also, might have role in experimental pain perception. African Americans had higher levels of pain in clinical conditions such as joint pain, and arthritis. Also, chronic pain center reported higher levels of pain unpleasantness, emotional response to pain, and increased pain behaviors among this nationality relative to whites [37].

Socio-political aspect: One of the enlightening questions that we asked was "What are the most effective pain killer drugs?" and "Are there any differences in the effectiveness of such drugs in different countries?" The answer to this question is a big challenge due to the unavailability of a reliable answer. By focusing on strategies that can impact personal medicine in developing countries, we may be able to identify some of the dimensions of this issue.

It is now clear that in any society, medication and prescription should be based on genomic data, data analysts and availability of reference datasets, retrospective and cohort studies. Because the genetic content of different ethnicities and races is different. Certainly what happens in a country, such as war, flood, earthquake or an epidemic disease, will be different on the epigenetic process and the response of people to drugs. Especially in the field of pain perception, which is different factors in people's approach to treatment. In countries that are in a war or are under sanction or have unstable politics, access to any healthcare may be difficult or even impossible and this can lead to an increase in suffering of the pain, even in very simple diseases [49].

Mülder, points out that, in personalizes medicine, developed countries have been more successful and favored than developing countries, because, wide-ranging literature and data bases on the genetic and environmental associations with diseases is available for Western populations [49,51].

Database systems are very important in improving health care system. Because they can provide an important way to monitor and improve the value of health services. This helps governments to have more oversight and see the medical process, and plan to finance health facilities. On the other hand, patients can expect better health care, improved efficiency, lower costs and better clinical decisions [52-54].

Also, drugs distribution and priced, are different in both developed and developing countries. Developed countries have made considerable progress towards growing admission to necessary medicines, but admission to essential medicines in developing countries is not sufficient. In countries for which there is information, the accessibility of medicines in the public sector is just one third, while private sector accessibility is about two thirds, and the prices people give for lowest-priced generic medicines differ from 2.5 to 6.5 times worldwide reference prices in these two sectors, respectively. New development in a number of countries shows that access to vital medicines can be better through stronger partnership among governments and civil society, which is sometimes out of reach of because of government policies [54].

In addition to the direct effects of politics on this issue, other factors that are caused by politics also interfere. The kind of drugs that used in developing countries might be different from developed countries due to this fact that the prevalence of some kinds of pain, such as headache, back pain and neck pain was slightly higher in developing countries than in developed countries, with unknown reasons [55-58]. The comparable data also showed that chronic pain conditions are common in the overall population world-wide [58,59]. Scientific evidence supports the hypothesis that less educated people in developing countries are more than developed countries suffered from disabling back pain, maybe because of less motivation and hopelessness or continue working to work as hard after an episode of back pain [59].

There are some drugs that could be beneficial for pain relieving but are forbidden in some countries such as drugs containing alcohol in Islamic countries or pain killers containing opioids. Other instance is morphine. “Morphine” distribution is extremely limited, or absent, in many low and middle-income countries [60]. According to the WHO data, only six developed countries accounted for 79% of total morphine consumption while all developing countries accounted for 6% of total opioid consumption despite developed pain treatment over the past two decades [61-63].

Reports show that in developing countries numerous immoral trials have been taken which led to death and increasing pain perception in people in trials without being subjected [64,65].

In addition, in developing countries, due to the lack of oversight by the ministry of health, weak diagnostics system, agricultural use and abuse of drugs changes the effective dosage of the drug and even causes the patient's resistance to the drug [66].

Medical equipment’s that are used in developing countries have distinct differences from those used in developed countries and the quality of diagnostic devices affecting the amount of pain in patients [67]. Whatever the device be more advanced and precise, the disease is recognizable in the early stages, and the treatment is easier to do, which prevents pain in patient in the advanced stages of the disease [67,68].

Physicians’ attention to opioids selection is another important factor in the patient’s response to pain. For instance, oxycodone might be a more potent to attenuating cancer-related pain, skin, muscle and visceral pain than morphine [63]. A mere glance at different countries health ministry indicates the relationship between precision medicine and politician’s point of view about this topic. For example in USA, the Obama administration back in 2015 launched its precision medicines initiative which was the official launch of precision medicine [69].

The great Britain also invested around 200 million euros in precision medicine back in 2015 and also launched new national genomic healthcare strategy in order to improve personalized medicine in 2020 [70].

In conclusion governments have significant role in precision medicine and can help to raise awareness about it and then change it to equitable policy and help it grow every day. Local governments can provide data about people and their life style; therefore accordingly it can make policies for creating big data toward achieving pain precision medicine. On the other hand in low and middle income countries, the rate of awareness is low following poor literacy [71,72]. Local governments also are in relation with non-profit organizations and can provide them with facilities in order to expand PPM [72]. Besides precision medicine indicates all involved criterias so genomic tests play significant role in pain precision medicine designed. Policies can help this kind of testing by providing enough budgets to help at least most of the society going through these kinds of tests specifically multigene tests. Also, PPM needs access to a large scale data in order to determine best mediation for individuals based on nurture and where they live. And the most important part is the rate of engagement. Governments can increase the rate of engagement by advertising and using social media in short apply according policies [73,74].

Genetic aspect: Polymorphism plays the main role in the diversity of pain perception in humans. Mutation in sodium channel proteins can significantly affect pain perception. 3 nonsense mutations, mutations that end the transcription, can cause loss of function in sodium voltage dependent channels. These channels are associated with inability to perceive pain. Therefore people with mutation in gene coding Nav proteins can perceive up to no pain. A recent study has shown the relation between hemiplegic migraine type 3 and mutations in a1-subunit of a different voltage-gated sodium channel. These results can demonstrate the importance of genomic factors in pain perception. Recent studies have shown mutations contributed to chronic pain. These mutations can affect

transcription regulators, receptors, cytokines, and also ion channels [75].

It has been accepted some factors such as Cytochrome P450 (CYP) activity that is involved in sensitivity of pain killers, varies between ethnicities and races. Approximately 10% of the Caucasian population carries a kind of CYP that is responsible for drugs poor metabolism [76]. Knowledge about Polymorphisms in Cytochrome P450 enzyme (CYP2D6,CYP3A4) [77-79]. That influence codeine's analgesic response, are determinative for dosage control [49,80].

Cytochrome CYP2D6 is responsible for the metabolism of 25% of all pain killer drugs, including codeine, hydrocodone, oxycodone, tramadol, and tricyclic antidepressants [49,81]. According to the documents, CYP2D6 has impact on phenotype of sedation after surgery and patient's response to post-operative pain drugs [82-84]. In this regard, identification of this gene family variation in each country among ethnicities and races could be effective for prevention of some adverse effects. For instance ultra-rapid metabolizers patients need more doses of methadone compared to slow or poor (an individual carrying no functional alleles) metabolizers [85,86]. In the other hand, they may die due to the toxic levels of morphine or over dose through metabolism of codeine to morphine [86-88].

Developing knowledge in different nationality about the functional polymorphism of the Catechol-O-Methyltransferase (COMT) gene that is responsible for regulation of dopaminergic and adrenergic/noradrenergic neurotransmission metabolism could be effective in management of pain drugs prescription. Zubieta, et al. [89] showed that patients with variation in COMT genotype had higher sense of pain and a higher density of mu opioid receptors in their brain. Therefore; variation in COMT genotype probably influences the human experience of different kind of pain such as heat hyperalgesia and may causes different variations in the responses and adaptation to pain and other stressful stimulation [89,90].

The polymorphism of ABC family is another factor that influence drugs destination. It is belonged to major super family of drug transporters. Polymorphisms of ABCB1 from this family can affect the pharmacokinetic and pharmaco-dynamic of opioids such as morphine, methadone, fentanyl, oxycodone and anti-inflammatory drugs [91-93].

The discussion about the polymorphic variation in the gene coding for pain related receptors cannot be negligible in this manuscript.

Since opioids are a basic choice in the management of cancer pain, opioid receptors including mu, kappa and delta that share a high degree of homology should be considered for exploratory genetic studies. Therefore, polymorphisms of the OPRM1gene, that code the μ-opioid receptor, could be the primary candidates for the receptors that evaluated efficiency of opioids [94,95]. There is relation between ABCB1/MDR1 and OPRM1 Gene expression. Thus, responses from poorest to highest to the opioid drugs depend to this polymorphism changes [95,96].

Detection of a wide range of noxious chemical, mechanical and thermal stimuli depend on Transient Potential Vanilloid (TRPV) channels receptor poly morphism that could result in pain hyper-senility. In this way, polymorphisms of TRPV2 and TRPV3 genes relation with fibromyalgia (a kind of pain syndrome) recognized in Korean population, despite the fact that TRPV2 haplotypes may have a protective role against this syndrome [97]. Also, another study revealed TRPV1 gene polymorphisms are associated with functional dyspepsia, a clinical syndrome accompanies by epigastric pain or burning, postprandial fullness among the Greek population [98]. As well as, it is suggested TRPV1 and TRVP3 might have role in the pain-related pathway of migraine between Spanish people [99].

Poly morphism in genes that control immune and inflammatory system is attractive for researchers. Complaining some patient about persistent pain after surgery could be related to homozygous SNP in the TNF-α gene that emphasis on the role of inflammatory factors and immune system on pain [100]. The other investigations reported patients with neuropathic pain possibly have a polymorphism in the TNF-α gene significantly more than pain-free people [101,102].

Non-Steroid Anti-Inflammatory (NSAID) drugs such as meloxicam or celecoxib created high volume of total prescriptions. Response to these batches of medications that their metabolism depended on arachidonic acid, CYP, renin angiotensin system, is another example for confirming role of gene in precisioning medicine. Because only CYP2C9 gene has more than 33 variants capable of modifying NSAIDs pharmacology. According to the data destination of NSAIDs in pain relief depends on CYP2C9 and/or CYP2C8 activity. Variants of these genes are associated with NSAIDs' side effects [103]. This difference makes changing courses or cause the hospitalization following cardiovascular or liver diseases, especially among European (there are not enough data in this case among developing countries) [104,105].

On the effect of genetic factors on pain-gender differences may be included in this group. In this regards it is noteworthy, females displayed a higher prevalence of chronic pain than males in developed and developing country [59]. Sensitization to pain might be moreover; arising from hormonal and its complications such as psychosocial factors, anxiety and depression [9,58].

Many painkillers are widely metabolized in the liver, so their destiny depends on the liver function. Liver damage may happen due to a wide range of events as well as a genetic form inherited [106,107]. Older people, especially if there is weak, hypertension, renal or liver disease are more at risk [108].

The Roadmap for Catch PPM

One of the goals of this manuscript was to introduce the reasons of need to formation precisioning pain medicine to governments that should invest in this regard. The second goal is to provide a solution and guideline to achieve the goal of personal treatment.

In order to help policy-makers implement the principles outlined here, and for those affected by these policies to embrace them, suitable frameworks are needed. Currently,

there are doctors, nurses, businessmen, biotechnologists, lobbyists and national health departments in many countries and many others who, through their own disciplines are making contributions to alleviating pain and suffering in locations all around the globe. Imagine, if you would, a metaphorical bus. The destination of the bus is a global health research and action center from where solutions to everyone's pain problems emanate. The bus needs to pick a route that allows it to pick up activists and stakeholders along the way and deliver them to the global center. At present, we have many potential participants in this project, but they need to be identified and engaged. In this day and age, creating the global center that is to be their destination is not difficult to establish since it can be, and may indeed need to be, virtual to begin with.

The following is an outline of a syllabus that we have conceived to further the cause of global PPM. It is a draught outline aiming to bring together the various stakeholders to establish a global network for the internationalization of personal pain medicine.

Discussion

Various stakeholders to establish a global network for the internationalization of personal pain medicine

- Public understanding of the origins of pain.
- Perspectives on PPM: Piece of a puzzle or links in a chain?
- Transitioning from a social view to a personal view of medical science and vice versa.
- Basic principles of personalized medicine; theory and practice.
- Economic perspective on PPM, including the economics of establishing PPM infrastructure (Short-term costs versus long-term benefits).
- The role of governance in PPM.
- The role of business in PPM.
- Modeling best practice and innovating new approaches to the implantation of PPM.

This outline needs to be consolidated with the help of stakeholders and the details of the content needs to be compiled and formalized. Even with genetic profiling, many different protocols are currently in use in different laboratories around the world. The harmonization process referred to here will involve the creation of standardized protocols. The identification of best practice and standardization of these procedures will help to make the data shareable which will help to make results compatible, enriching the global database and reducing measurement errors. We then need to encourage the business and research community to adopt those protocols.

Create a global database

Various countries are creating genetic profile databases, especially in relation to criminology. For the purpose of developing a PPM database, existing systems have a number of shortcomings. In the first instance, there is a big difference between using genetics to identify people and using it to address individuals' physiological strengths and weaknesses. Secondly, there is a lack of global standards for such protocols. Furthermore, as we have pointed out here, genetic information by itself is not enough where medicine is concerned since the environment and the consequent epigenetic changes play an important role in our response to treatment. Finally, our genetics, epigenetics and medical history needs to be matched against a database of treatment protocols, including medication.

Make the data accessible to research community

Without data, there can be no science, no scientific discoveries and no scientific progress. The quality and quantity of data are the primary determinants of the reliability and validity of research findings. We believe that a global database of the type suggested in Stage 8 can transform the medical sciences in the same way that the availability of physical data tables transformed the physical sciences. Here, we have settled on the word 'roadmap'. The roadmap presented here was developed through consultation with clinicians, scientists, psychologists as well as specialists in education research, information technology and management (**Figure 1**).

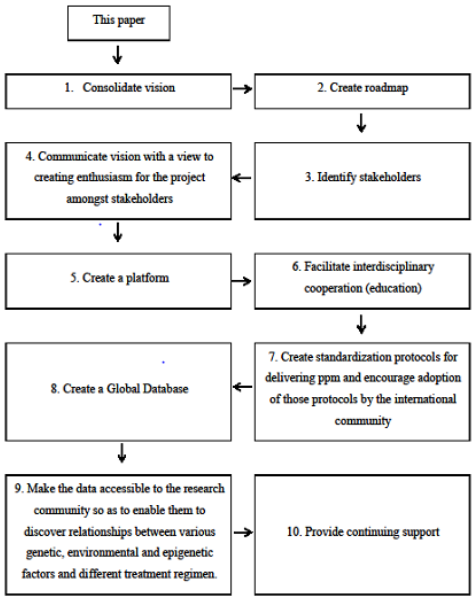

Figure 1: A proposed roadmap for the creation of a global center for PPM.

Future Perspectives

In the general view of the studies that have been done so far and examining the factors involved can be said though genetic factors are one of the main factors involved in the precisioning pain medicine, but the role of epigenetic and political mediators cannot be ignored. If there were no political issues, we might have seen these differences much less. In addition to political issues, cultural and social issues that influenced on epigenetic should not be ignored, which requires more study to examine the impact of each of them. Such as time to visit clinic due to hard pain depend on the culture and attitude of society to the pain resistance can change the trend of disease.

Conclusion

In conclusion, there are many blind spots in the medical sector of precisioning pain, especially in developing countries, which need to be found and their effects determined because the personalize pain medicine knowledge is helpful for producing data-based clinical guidance and reducing cost of treatment.

The identification of best practice and standardization of these procedures will help to make the data shareable which will help to make results compatible, enriching the global database and reducing measurement errors. We then need to encourage the business and research community to adopt those protocols.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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