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Application of P4 (Predictive, Preventive, Personalized, Participatory) Approach to Occupational Medicine[1]

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Summary

In recent years there has been a growth in the role of prevention in controlling the disease burden. Increasing efforts have been conveyed in the screening implementation and public health policies, and the spreading knowledge on risk factors reflects on major attention to health checks. Despite this, lifestyle changes are difficult to be adopted and the adherence to current public health services like screening and vaccinations remains suboptimal. Additionally, the prevalence and outcome of different chronic diseases and cancers is burdened by social disparities. P4 [predictive, preventive, personalized, participatory] medicine is the conceptualization of a new health care model, based on multidimensional data and machine-learning algorithms in order to develop public health intervention and monitoring the health status of the population with focus on wellbeing and healthy ageing. Each of the characteristics of P4 medicine is relevant to occupational medicine, and indeed the P4 approach appears to be particularly relevant to this discipline. In this review, we discuss the potential applications of P4 to occupational medicine, showing examples of its introduction on workplaces and hypothesizing its further implementation at the occupational level.

Introduction

P4 medicine is a new paradigm in the healthcare panorama which aims to enable a comprehensive medical approach, by using a large network of information on health and disease, and through the single individual profiling based on "-omics" data [1]. A major proponent of this paradigm is L. Hood, who has been long involved in the delineation of a holistic view of medical science and cancer biology, with particular focus on genome sequencing and correlation of genetic variants with wellness and disease phenotypes [1].

Each "P" individuates a milestone: predictive, as focused on the early identification of potential diseases; preventive, as connoted by the targeted prevention of the disease based on its prediction; personalized, as it conceives the individual as unit of diagnosis and treatment; participatory, as each individual is responsible for optimizing their health. Compared to common medical practice, P4 medicine comes to be characterized by the following traits:

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proactive rather than reactive; interested in the prevention of the disease and its regression at the early stages, rather than treatment; individual-oriented in addition to population-oriented; focused on wellbeing rather than disease; data-driven, with the building of personalized "data clouds"; based on the deep phenotyping of subjects; aimed at both body and mind, with attention to psychological and cognitive wellbeing [1]. Indeed, P4 medicine, which is part of system medicine, requires the generation of a vast database of information on factors associated with the health and disease of the individual. Big data system would collect socio-demographic, biological and genetic information in order to make a comprehensive medical database. This database would characterize both health and disease status of the individual, offering the possibility to observe the shift from one to the other, and consequently to recognize the alarm signs of disease occurrence [1,2].

In this regard, genome, metabolome, proteome, transcriptome which are included in the "omics" pools would be particularly precious sources of information. The disposal of genetic data on a population level would lead to the identification not only of genetic diseases on a hereditary basis, which are the large minority of the pathologies, but to the description of clusters of polymorphisms and mutations which together correspond to higher likelihood of disease. Next to this, finds place the development of biological networks. These allow the description, through sophisticated algorithms, of the pathways that characterize the transition from health to disease [2]. In addition, system medicine aims to the identification of relevant biomarkers which may be used to better understand the physiopathology of a disease as well as its early diagnosis [2].

Phenotyping is one of the main points of P4 medicine, which is built on the detailed profiling of the health status of each individual. This passes through the measurement of biochemical [e.g., blood tests] and physiological [e.g., blood pressure] parameters, genetics [e.g., genome, microbiome], as well as the evaluation of the exposure to risk factors [e.g., pollutants, occupational factors, biological agents] [3]. Few large databases make this kind of information available at the moment, such as UK Biobank, allowing to conduct relevant epidemiological and clinical research with a precious source of genomic data [3].

The occupational physician would represent an important figure in data collection, preventive protocols design and introduction, and improvement of health education.

EXAMPLES OF P4 MEDICINE

Vaccinations

Vaccination is an example of P4 medicine where the occupational physician could play an important role. Vaccinations are predictive and preventive, because herd immunity allows the protection of millions of people, even unvaccinated [e.g., immunocompromised], from infectious diseases [4]. Indeed, vaccinations represent the typical example of preventive intervention whose benefit occurs mainly at the population level. Moreover, they help controlling the spreading pressure of antibiotic resistance by scaling down the infection rate. Second, vaccination is strictly participatory: the single individual is responsible for the choice of vaccination uptake, including children's administration. This raises one of the main issues around vaccination, as adherence to vaccination campaign and prevention of infection such as diphtheria, tetanus, pertussis, polio (DTP), Haemophilus influenzae type B, measles, mumps, rubella, hepatitis B [5], seasonal influenza [6], as well as Human Papillomavirus [7] remains suboptimal, even in those countries where vaccines are promoted and freely offered to the general population [5-7]. This is largely due to the lack of perception of the individual benefit from vaccination [8]. Nevertheless, not only vaccines are accompanied by large-scale benefits, but they also provide individual health improvements, most of which can be seen after a long time. For example, an inverse association has been reported between Alzheimer's and DTP or flu vaccinations [9]. Also, it has been hypothesized that the lower susceptibility of children to COVID-19 infection can be related to the immune competence developed following vaccinations undertaken in early childhood [10]. Lastly, vaccines could be personalized: starting from the assumption of an overall benefit of vaccination to prevent communicable diseases, the possibility to offer targeted recommendations based on standardized algorithms of the anamnestic data of each individual would lead to a more accurate exclusion of the subjects for whom benefits would be lower than risks [11]. These issues have become highly relevant in the current pandemic circumstances with the controversy around the administration of multiple newly developed COVID-19 vaccines, with differences in composition, timing of administration, effectiveness and potential adverse events [12]. The use of artificial intelligence (AI) has been particularly important in the implementation of the offer of COVID-19 vaccines to specific target of the population, e.g. by category of workers. Specifically, healthcare workers have been the first category of workers to be addressed by the new vaccine, which has now been made mandatory in hospital settings in many constituencies [13].

Surveillance of COVID-19

The COVID-19 emergency demonstrated how data network and monitoring can be crucial in healthcare. All over the world it became clear how technology could support pandemic response, with AI being applied in diagnosis, management and therapy of the infection [14]. Among the wide-range interventions developed through AI was the tracking of individuals and contacts [15-17]. In particular, migration maps collecting real-time data on location and movements have been applied to people who had visited the Wuhan market, where the infection spreading started [17]. Machine learning models have been developed to forecast the regional transmission dynamics [17]. On the other hand, digital health initiatives can amplify inequalities and contribute to healthcare disparities [17], since technologies may not be equally available and affordable by all population groups, and their being essential would leave some strata of population excluded in any case (e.g., older people not using smartphone, people living in isolated settings) [18, 19]. The effectiveness of intervention gained by using technologies in managing the COVID-19 situation has been shown in multiple settings. Indeed, countries that have quickly deployed digital technologies to facilitate planning, surveillance, testing, contact tracing, quarantine, and clinical management have greatly reduced the burden [17].

Table 1 shows examples of how different countries expoited digital technologies during the pandemic. For example, countries like China, Singapore, Sweden, Taiwan and USA expoited different digital technologies for the process of infection tracking, like data dashboards, migration maps, machine learning, real-time data from smartphones and wearable technology. Similarly, a variety of tools, such as digital thermometers, mobile phone applications, thermal cameras and web-based toolkits, were used to identify potentially positive subjects,

Table 1. Exploitation of different digital tools during COVID-19 pandemic worldwide

Digital tools	Application	Countries
Tracking	Data dashboards; migration maps; machine learning; real-time data from smartphones and wearable technology	China; Singapore; Sweden; Taiwan; USA
Screening for infection	AI; digital thermometers; mobile phone applications; thermal cameras; web-based toolkits	China; Iceland; Singapore; Taiwan
Contact tracing	Global positioning systems; mobile phone applications; real-time monitoring of mobile devices; wearable technology	Germany; Singapore; South Korea
Quarantine and self-isolation	AI; cameras and digital recorders; global positioning systems; mobile phone applications; quick response	Australia; China; Iceland; South Korea; Taiwan
Clinical management	AI for diagnostics; machine learning; virtual care or telemedicine platforms	Australia; Canada; China; Ireland; USA

Adapted from [17]
AI, artificial intelligence

and mobile phones were also used for geolocalisation as real-time monitoring devices, helping the contact tracing [17].

Iceland and South Korea are countries in which complex AI-based strategies have been developed from the beginning of the COVID-19 epidemic. Iceland, addressed the pandemic with the widespread testing of asymptomatic subjects. Mobile technology was used to collect data on patient-reported symptoms, and combined with other datasets [e.g., clinical and genomic sequencing data] to reveal information about the disease and the infection's spreading. All in all, this contributed to the knowledge on the prevalence and transmission of asymptomatic COVID-19 [17].

Aggressive contact tracing was the strategy undertaken by South Korea's government: security camera footage, facial recognition technology, bank card records, and GPS data from vehicles and mobile phones were used for the strict monitoring of potential contacts between infected people. In this way, real-time data and detailed timelines of people location and movements were collected. Also, emergency text alerts about new COVID-19 cases in their neighborhood/area have been sent to sensitize people to be careful in their social habits, and potential contacts were instructed to report to testing centers and self-isolate [17]. As a consequence, the mortality from COVID-19 in these countries has been very low (Table 2).

Artificial intelligence and disease prediction

Artificial intelligence (AI) has been widely studied and applied for public health surveillance to predict disease outbreak and evaluate disease surveillance tools [21] AI-driven health interventions fit into four categories relevant to global health researchers: (i) diagnosis, (ii) patient morbidity or mortality risk assessment, (iii) disease outbreak prediction and surveillance, and (iv) health policy and planning [21]. Approaches based on expert planning and household survey data have been developed to optimize community health-worker visit schedules [22]. Additionally, AI methods aimed at informing program planning efforts within facilities have been evaluated in low and middle-income settings, including forecasting the number of outpatient visits at urban hospitals and the length of health retention [21]. Machine learning and data mining have been also used to estimate road safety, helmet use and predict road injury severity [21].

The identification of the determinants of a disease at the population level is a prerequisite to predict and prevent its occurrence in the single individual, providing the rationale for targeted and specific treatment [23]. The availability of big data clouds would help the design of public health interventions to be compared through clinical trials with the aim to develop effective standardized protocols. This would be of major importance in the health surveillance at the occupational level. AI-based screening programs have been implemented for early polyps and colorectal cancer detection [24-26], diabetic retinopathy [27], atrial fibrillation [28], chronic obstructive pulmonary disease (COPD) [29], low back pain [30], among a high variety of diseases.

To build effective prediction models of disease occurrence, the use of standardized questionnaires and other tools to measure health and wellbeing is needed, in order to conduct large perspective population-based studies. Indeed, the controlled collection of large amounts of data provide the possibility of high-quality estimates and risk assessment [31, 32]. The building of effective predictive model is a complex endeavor, as it requires the integration of multiple machine learning approaches in order to develop a single algorithm describing a specific disease [33]. For example, phenotypes of COPD have been classified through machine learning method, helping in the understanding of the biological mechanisms underlying this disease [34].

Table 2. Cumulative COVID-19 rates/100,000, as of November 18, 2021

Country	Incidence	Mortality
Iceland	4,460	9
South Korea	779	6
USA	14,282	231

Source [20]

Malaria and Zika virus have been monitored and controlled through algorithms generated by using machine learning systems and AI with high accuracy [21]. Indeed, the field of communicable disease is one of the most suitable to exploit the potential of AI, being the tracing of infected individuals fundamental to limit the spreading of infection. This have been observed for influenza virus, as well as for HIV, tuberculosis, malaria, dengue, addressing issues of major concern in low- and middle-income countries, where AI takes the shape of a new powerful weapon for public health [18].

Other examples of successful machine learning and AI applications include the prediction of the risk of perinatal risk factors and adverse events, high-risk sexual behaviors among adolescents, children at risk of missing scheduled vaccinations, risk of failure of anti-tubercolosis treatment and risk of cognitive sequelae after malaria at pediatric age [18]. Moreover, signal processing methods have shown to be effective in detecting cervical lesions starting from microscopy or images of the cervix ("cervigrams") with an accuracy greater than 90% [18]. Deep learning histopathology identifies metastatic breast cancer in sentinel lymph node biopsies, and is able to differentiate malignant from benignant skin lesions, with correct diagnosis of basal cell carcinoma in >90% of cases compared to experts [35]. Finally, chronic diseases such as diabetic retinopathy, depression and congestive heart failure can be predicted with high sensitivity and accuracy, representing a valid support to precision medicine [35]. Additional examples of application of AI to different health domains are listed in Table 3.

Application of P4 to Occupational Medicine

Figure 1 summarizes the possible applications of precision medicine to the field of occupational health. Although we organize this section according to the four components of P4 Medicine, there is substantial overlap between them, owing to a comprehensive nature of the approach.

Predictive

Occupational medicine is predictive in its aim of designing a specific risk profile for each worker. This goal could be reached through the combination of genetic testing, family and medical history, work history, lifestyle and general health information of the individual worker. The data clouds so obtained for the single individual could be stratified by occupation, working load and working activities as well as occupational exposures, creating job-specific health datasets. The characteristics of the different datasets could be compared, possibly leading to the identification of risk factors or subgroups of susceptible workers for a specific occupation. The data could also be used as input for the generation of algorithms through machine learning methods, possibly integrating traditional diagnostic tests.

In a recent study, comparable results have been obtained by using either online machine learning audiometry procedures or conventional manual threshold-estimation procedures [40]. In particular, this technique provided fully predictive hearing function estimates in significantly less time than the Hughson-Westlake procedure, also adding

Table 3. Examples of application of artificial intelligence (AI) to different domains of medicine. Adapted from [21].

Domain; country [reference]	Types of AI	Outcome
Diagnosis; global [36]	ES, ML, NLP, SP	Tuberculosis
Risk assessment; Thailand [37]	DM, SP, ML	Dengue fever
Outbreak prediction; global [38]	DM, ML, NLP, SP	Zika virus
Health policy; South Africa [39]	EP, ML	length of stay in the practice of HCW

ES, expert system; ML, machine learning; NL, natural language processing; SP, signal processing; DM, data mining; HCW, healthcare workers

Figure 1. Application of P4 to occupational medicine

audiogram details not provided by other methods, such as continuous-frequency threshold estimates and continuous-frequency psychometric spread estimates. According to the authors, this approach should be integrated in the standard audiologic workup as it can efficiently sum up in a single procedure different audiometric tests.

The prediction of personal risk would lead to the optimization of the employer's resources in targeting prevention of occupational diseases not only on the basis of risk factors, but also on workers' individual characteristics. Clearly, this strategy implies an increase of the economic investments in the well-being of the worker, but with overall savings in the long period.

Preventive

A better understanding of how personal characteristics confer a different level of susceptibility to occupational risks has implications in the evaluation of permissible exposure levels. The association of DNA damage and particular levels of exposure to a carcinogen agent can differ based on individual susceptibility [41]. The identification of biological and molecular pathways at the transition from health to disease would contribute to prevent relevant genetic or epigenetic alterations involved in occupational carcinogenesis, and the malignant transformation of preneoplastic lesions, as well as the worsening of chronic non-malignant diseases [42]. By describing these associations, preventive strategies could be targeted to individuals at higher risk of a specific disease when exposed to a potential risk factor, for example subjects with predisposition [genetic, or resulting from previous occupational history] to bladder cancer who smoke could be excluded from jobs entailing exposure to fumes and aromatic amines, and would particularly benefit from behavioral and educational intervention to stop smoking [43].

The identification of gender-specific risk factors, based on exposure and opportunities for prevention [e.g., cancer screening] could improve health and wellbeing at the workplace [44]. Similarly, system medicine could favor the development of age-specific programs in light of the frailties and specific changes in biological and chronological age. This is especially important given the ageing of working population [45]. Precision medicine uses risk assessment to identify subgroups at higher risk of negative outcomes [disease, adverse events, falls], targeting intervention on this basis [46].

Personalized

In addition to physical health, a P4-oriented occupational medicine would focus on mental wellbeing, with consideration to [i] social characteristics [marital status, family, social network, economic status, housing], [ii] lifestyle factors [alcohol, smoking, diet, physical activity, sedentary lifestyle], [iii] lifetime events [change of residence, change of job, separation, bereavement], and [iv] interaction between determinants, including host factors. Putting together the different information of the single individual, a subject-specific profile could be defined in which susceptibility to a risk factor can be accurately estimated and adequate measures can be adopted to minimize risks [41]. Risk assessment can indeed benefit from precision medicine by generating risk estimates leading to evidence-based recommendations for different outcomes [41], including data on family health history [46]. Also, the approach of precision medicine on the single individual would lead to the accumulation of evidence on multiple exposures and consequently describe the short-term and long-term responses of the organism to changes which occurs from exposure to environmental and occupational agents [41].

The personalization of occupational medicine could also have a role in guiding the choice of working career: the career path of the individual could be recommended based on the predicted risks and the working activities required in the specific setting or occupation.

Participatory

The occupational physician could develop programs aimed at encouraging the adoption of healthy lifestyle habits based on one's own risk profile, improving the health education of the working population.

The collection of detailed health information and biological samples to build genomics phenotyping and the introduction of health protocols require the active participation of the worker. Indeed, P4 occupational medicine demands the willingness of the individual to provide in-depth data on their state of health and general wellbeing, and to perform tests to define their own phenotyping [1]. Moreover, this information should be updated periodically. A possibility would be the use of mobile apps [47], as well as online questionnaires offered through the professional e-mail [48]. Also, the worker should be directly involved in expanding their knowledge of health and wellbeing in general, with personal investment in risk prevention and in adopting healthy behaviors involving lifestyle modification and adherence to therapies [49-51]. Finally, in a P4 approach to occupational medicine, individual workers are asked to be made aware of their own specific risks, thus requiring a conscious acceptance of one's own risk profile [52].

Examples of applications of P4 to occupational medicine

Following the P4 model, the occupational physician could complement the workers' health surveillance with machine learning reading systems. In this regard, the application of AI would be helpful in predicting with high accuracy the onset of occupational disease, occurrence of long-term sequelae and worst outcome, also identifying those subjects who will have great benefit for preventive interventions.

Among the large-scale impactful intervention at the workplace, there are the ones targeting cardiovascular and metabolic conditions. Body mass index (BMI) reduction [51, 53, 54], blood pressure control [54, 55], and lowering of cholesterol [54] and glycemic levels [54] have been widely addressed outcomes in occupational medicine programs. An example is the ChooseWell 365 Randomized Clinical Trial, conducted between 2016 and 2018 among healthcare workers (HCWs) with the aim of controlling BMI in a hospital setting in Boston, Massachusetts [51, 56]. A first study on 297 HCWs consisted in the retrospective collection of cafeteria sales data of the previous 3 months in order to register a real-time assessment of food choices via tracing of quantity, quality and time of purchases, together with information from a self-reported questionnaire on dietary habits and cafeteria purchases [56]. A first analysis investigated the genetic factors involved in dietary behaviors and weight control [56]. Genome-wide polygenic score (GPS) accounted for 20% of BMI variation [56]. In particular, high GPS was associated to BMI, food choice behaviors, low dietary quality at the workplace, higher purchases workplace, lower likelihood to prepare dinner at home [56].

Another analysis from this study described the effects of introducing an automated behavioral intervention build on the basis of employees' cafeteria purchasing data [51]. These were used to develop a personalized intervention among 602 HCWs [51]. In particular, the intervention group received two mails/week with information on previous cafeteria purchases and healthy lifestyle recommendations, plus one letter per months with peer comparisons and financial incentives for healthier behaviors. No difference in BMI change was registered among intervention and control group, but the intervention led to improved food choices, with increased green-label purchases. The authors suggest the use of employee cafeteria purchasing data can help in the development of a personalized intervention among HCWs [51].

Another example of P4 in occupational medicine regards the use of machine learning to manual handling of loads [57]. Technological tools have been developed to detect and measure fatiguing tasks during working activities [57]. Baghdadi et al. have recently described the use of a device measuring the kinematics of gait cycles by using an inertial measurement unit (IMU) during physical tasks [57]. The reported method uses a template matching pattern recognition technique, along with machine learning algorithms for classifying fatigued status during walking using an IMU attached to the ankle. This device obtained data which helped in detecting lower muscle fatigue, an important risk factor for falls due to postural instability. This offered a practical framework for predicting fatigue from manufacturing tasks. This kind of measures, once associated to movements, could identify tasks are represent a higher risk for the worker [57]. The validation of such measurements could translate into recommendations or improvement of the working environment in order to reduce the occurrence of injuries due to fatigue.

With regard to return to work (RTW), evidence comes for example from a study conducted among 2000 Korean workers (1412 RTW group, 588 non-RTW group), leading to the building of a predictive model for RTW after sick leave by using a machine-learning algorithm [58]. To do this, a gradient boosting machine (GBM) consisting of 59 different variables was used. The predictive variables were selected by experienced board-certified occupational and environmental medicine doctors, based on individual (e.g., sociodemographic characteristics, having a qualification, being covered by insurance), work-related (e.g., employment status, previous working period), injury- and compensation-related (e.g., sustained contact with the original workplace, extra reward in addition to workers' compensation, provision of rehabilitation programs), and psychological factors (e.g., self-esteem, self-efficacy). The GBM showed excellent performance in the binary classification (returned to work vs not working), while suboptimal performance was described in differentiating the form of RTW [58].

P4 medicine can also be applied in the context of chronic pain, a condition with high prevalence possibly leading to opioid use and adverse events which imply absenteeism or reduced working productivity [59]. Pain cannot be directly measured, but it is rather self-reported, measured through scales as visual analogue scale and the numeric pain scale, or by using multidimensional approaches [59]. The overlap between chronic pain and poor psychological wellbeing has been widely studied and there is evidence of how body sensation affects emotions [60]. A recent study has measured the intensity of the pain reported by a group of workers, together with the description of 11 emotional states, and the corresponding body locations in order to predict pain two weeks later through a machine learning approach [59]. This led to models that identified body maps of fatigue with negative emotional state as well as positive emotional state with past pain as best predictors of future pain, thus showing the contribution of emotional experience to physical pain, helping in the understanding of its mechanisms.

The development of a comprehensive database collecting information on occupational disease is fundamental for the practice of a P4 approach: such a dataset not only would systematically collect data leading to the accurate description of the occurrence of occupational diseases, but with the integration of work history, genomic, lifestyle, sociodemographic and clinical data of each worker – even without the occurrence of any condition possibly linked to working activity – a deep investigation of the determinants of the occupational diseases would be possible, also leading to the description of the biological networks underlying their onset [41]. The accurate epidemiological knowledge of work-related conditions and on working population overall will enable to set targeted intervention aimed at promoting health and improving the effectiveness of current surveillance protocols [41].

It follows that the identification of workers with greater benefit for preventive intervention would be possible. Moreover, by assessing the impact of interventions which promote health and wellbeing it would be possible to improve the adherence to screening protocols in specific occupational settings.

Limitations and perspectives

The application of P4 medicine is not without limitations (Table 4) [61]. The introduction of such a model would need enlightened leadership to make it accepted and widely adopted [1]. Another possible barrier is the intrinsic inertia of the healthcare industry, which is difficult to be overcome. This was seen even in the management of the COVID-19 pandemic and the introduction of the use of personal protective equipment first, and vaccination later [62, 63]. On the other hand, single-payer systems (e.g., countries with a national health system) offer a better opportunity for development of P4 in occupational medicine. A major difficulty lays on the fact that P4 medicine requires to educate healthcare professionals, patients, regulators and payers as to the nature of wellness-centric medicine [33].

In a historical timeframe which is connoted by the fast spreading of information, and the raising of different branches of medicine including homeopathic or natural, it is of outmost importance

Table 4. Barriers and perspectives of P4 applied to occupational medicine.

Barriers	Perspectives
Short-term costs	PRS score for occupational cancers
Need for enlightened leadership	Machine learning for early diagnosis of occupational cancer
Worker's privacy issues	
Spreading of skepticism due to misinformation	Personalized therapy in targetable mutations
Low profile of occupational physician	

to overcome the skepticism about prevention [64]. Fortunately, the prevention and reversal of the earliest chronic disease transitions are more and more becoming a fundamental part of healthcare. Indeed, P4 medicine configures as a possible evolution of the recent medical effort, mainly driven by public health.

A major barrier is represented by legal constraints about gathering individual health data [65]. Indeed, the share of personal information is a personal choice, and should be protected [65]. This represents a major concern in the occupational setting, where risk assessment and health surveillance may raise conflicts between employers and employees. Indeed, the worker needs to understand the usefulness of their data, both for themselves, their household, and the community at large. A system medicine accessing detailed and large-scale personal data needs to make the same data available to stakeholders, including the individual from whom data originated, with careful control of data de-identification during collection, storage, analysis and result dissemination [65].

Besides this, it is intrinsic to preventive medicine the misperception of not only the entity of the health benefits, but also the costs sparing. Failure of both payers and providers to understand the enormous potential savings of wellness-centric medicine represents a major barrier to its implementation [1].

Lastly, it has to be taken into account that the low prestige of occupational physicians and other public health professionals remains one of the possible limits in the introduction of P4 medicine on a large scale [1]. Personalized cancer prevention represents an area of potential application of P4 approach at the occupational level. A useful framework for personalized cancer prevention has been developed by Rebbeck and colleagues [66]. These authors distinguish four levels of preventive interventions. The first level if the population-approach, in which the unselected population is the target, and the strategy is based on modification of norms and laws. Examples of this approach are the interventions to reduce tobacco smoking, or the implementation of vaccinations against oncogenic viruses such as HPV. The second level comprises interventions targeted to individuals at elevated risk, such as low-dose CT-based lung cancer screening for heavy smokers. Precision cancer prevention, which represents the third level, is based on mechanism-derived interventions targeted to subjects at very high risk, such as carriers of high-penetrance mutations [e.g., oophorectomy in BRCA1/2 mutation carriers] or subjects with preneoplastic conditions. The final level is that of precision medicine, in which cancer patients with targetable mutations are offered personalized therapies.

While most approaches for precision prevention are based on individual high-risk genes, a growing attention has been paid in recent years to the combination of large numbers of gene variants, each contributing a modest excess risk. The combined effect can be expressed as a polygenic risk score (PRS) [67]: each variant contributes positively or negatively to the score according to the known association with the outcome of interest. It has been shown that subjects with extreme values of PRS (e.g., top 1%) experience a 3-5-fold increased risk of breast cancer, approaching that of carriers of high-risk genes [68].

While prevention of occupational cancer has been historically based on population-level approaches, the opportunity of more personalized intervention can be now considered. Studies aimed at identifying genetic profiles that would put workers at increased risk even from low-dose exposure to carcinogens should be conducted. This has been done for lung cancer and tobacco smoking [69] and indoor air pollution [70].

Conclusions

P4 medicine represents a new paradigm, encompassing multiple trends that are taking place in medicine. While not all components of P4 can be immediately implemented in any particular healthcare setting, this approach is helpful to drive innovation and setting future priorities. Application of P4 to occupational medicine has so far been limited; yet we think it offers a novel framework for the discipline, which may in turn result in the recognition of occupational physicians as drivers of medical innovation and wellbeing promotion.

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