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Review Article

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Ethical Approaches in Secondary Findings Report from Exome Sequencing Analysis

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Abstract
In Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) approaches, incidental findings (IFs) or more precisely secondary findings (SFs) have indicated controversial reports. To address SFs issues, well-known guidelines have been released such as the versions of the American College of Medical Genetics and Genomics (ACMG); however, when, to whom, why, and how these SFs should be reported are the key questions that need to be addressed ethically. The current review aimed to investigate the papers with a focus on the ethical approaches regarding IFs/SFs. In this comprehensive review, we searched the PubMed database for related publications, and 58 papers were selected as the narrowest reports. There was a positive tendency to disclose the SFs by the professionals and an enthusiasm in patients to be informed about all of their genetic reports. Several studies have addressed that guidelines could not cover all aspects of IFs/SFs ethically and medically. The main focus of these studies was the modernized opt-in informed consent according to some items including prenatal/post-natal or pediatric/adulthood issues. Other foci are genetic variant clinical actionability, cancer status, population-based backgrounds, time- and cost-effectiveness, the education level of subjects and clinicians, and the combinations of pharmacogenomics findings to introduce medicinal treatments and personalized prescriptions leading to more suitable healthcare. Altogether, concerns remain about the ethical approaches in the SFs; however, the present review introduced remarkable solutions which will be ethically and practically possible to be utilized. This review also found that recent reports are concentrated on the high-volume Exome Sequencing tests of subjects from biobanks and healthcare centers.

Keywords:
incidental findings; secondary findings; exome sequencing; acmg recommendations; ethics; genetic

1. Introduction

In the context of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)z, incidental findings (IFs) have been a controversial topic. An IF of secondary finding (SF) is typically described as a finding regarding a specific research result that has prospective relevance to health or reproduction and is identified during research but it is not in the scope of the study [1]. “However, as Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES) become more prevalent in clinical settings, concerns have grown to include findings that, while personally significant, are unrelated to the primary therapeutic purpose of the sequencing.” The American College of Medical Genetics and Genomics (ACMG) released a guideline on the points to consider in the clinical utilization of genomic sequencing in 2012. The guideline cautions that when interpreting secondary findings (SFs) or results uncovered during the screening of asymptomatic individuals, the criteria for what is deemed reportable

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must be stringent to avoid overwhelming the healthcare system and individuals with potentially large numbers of false positives [2]. Consequently, the ACMG established a working group to make recommendations on how to handle IFs in clinical sequencing [3].

In March 2013, the working group published a list of recommendations for reporting IFs in clinical exome sequencing (CES) and genome sequencing (GS) [4]. On one view, the recommendations took severely the need to limit IFs to solely those with obvious clinical relevance and actionable results. They offered a meticulously selected list of particular variants that, in their opinion, must be clinically reported. On the other view, the enthusiasm with which these variants were chosen appears to have inspired the Working Group toward making decisions that dramatically deviate from current practice and policy.

"Initially, the recommendation was that clinical sequencing laboratories should be responsible for thoroughly searching for the variants specified in the guidelines and including these findings in clinical reports, rather than focusing solely on the intended objectives of the clinical sequencing. Additionally, the guidelines advised against considering patient preferences when reporting these results." In other words, regardless of whether the patients or their caregivers want the details, everyone should receive all the suggested results. Especially, sequencing on children is included in this guideline [3]. While the professionals agree with the Working Group's desire to respect beneficial effects by giving the patients any information that may improve their future medical care, they find the recommendations hard to implement from both an ethical and a practical standpoint. They not only questionably reinterpret IFs but the inference that physicians should override individualized autonomy for the patient's 'own benefit' is barely supported in current clinical ethics [3].

2. Materials & Methods

Based on both lacking a gold standard guideline to cover all ethical approaches and the increasingly various viewpoints of clinical professionals (geneticists, lab experts, and physicians), in the current review we searched the PubMed database comprehensively for literature on the IFs or SFs from 2011 to 2023. To get a deeper view of the ethical issues resulting from SFs, the present study aims to categorize the concerns as the causing factors and introduced the solutions for future guidelines to use these recommendations. In summary, considering the initial reports and the issues which recent reports are struggling with them, there are some solutions for SFs disclosure with higher priority that need to be focused including professionals' standpoints, patient education, personalized opt-in decisions, cancer status regarding somatic and germ-line reports, pharmacogenomics approaches, clinical actionability of the SF genetic variants, and financial issues.

3. Results

3.1. Concerns

The concerns of reporting IFs/SFs include informed consent, controversial reports, penetrance of IFs/SFs variants, lack of functional studies, true positive versus false positive IFs/SFs, and Costs (Table 1).

3.1.1. Informed Consent

The variety of recommendations and consent forms, as well as the inclusion of controversial statements and criteria, result in a non-standard policy for IFs/SFs. However, only a few reports have examined the practical application of policy standards for IFs/SFs, with an emphasis on existing reporting procedures in the framework of clinical ES. An investigation conducted in the United States discovered a wide range of policies concerning the range of reportable IFs/SFs (which are much beyond the ACMG list) and various opt-in and opt-out options [5]. The information produced by genome sequencing will be both health-associated (present and future) and non-health-associated. Along with information related to medical manifestations for testing on an ES/GS platform, they are as follows: gene-variant carrier condition, which might have effects on reproductive decision-making; data on disease vulnerability or predisposition; data about ancestry that may have medical value in the future; and detection of previously unknown disorders. A few phenotypes might allow for narrowed targeting, whereas others (for example, intellectual disabilities or autism spectrum disorders) might make the bulk of the exome available for analysis. Modern methods are used in both prenatal and postnatal contexts in addition to both somatic and germ-line examinations. IFs might be as essential to a family as they are to a person in some situations. A significant emphasis is made on circumstances in which the laboratory and clinician are given data that appears to be irrelevant to genes known to be connected with the trait that prompted screening. These circumstances are as follows:

1. A medical geneticist or an associated genetic counselor should provide counseling before beginning ES/GS, and formal patient consent should be included;
2. IFs/SFs found in either children or adults might be of significant clinical relevance, for which there

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Table 1: The concerns regarding SF reporting with brief descriptions.

Item	Description
Informed consent	The variety of recommendations and consent forms, as well as the inclusion of controversial statements and criteria, result in a non-standard policy for IFs/SFs.
Controversial reports on the variant	The differences between the guidelines reports and some reports on a common SF report.
The penetrance of IFs/SFs variants	Lack of specifying the lower and higher penetrance in the age group and between cancer and non-cancer patients.
Lack of functional studies	Lack of complementary functional investigations of some reports; especially case reports which are growing fast.
True positive versus false positive IFs/SFs	More replicative reports of precise clarifying of a clinical condition caused by a variant lead to a higher threshold of positive findings. This issue will emerge when there is not adequate clinical data, and the reports will have resulted from only computational predictions.
Costs	There are several concerns about the extra expenses on the healthcare system from interpreting the data to proving the reports and additional time for counseling.

IFs: incidental finding; SFs: secondary findings.

are treatments to lessen or avoid disease intensity. As part of the informed consent procedure, patients should be made aware of this capacity;

3. Pretest counseling should address the predicted results of the test, the chance and types of IFs which could be produced, and the sorts of outcomes that will or will not be reported. Patients should be informed whether and which sorts of IFs might be sent back to their referring doctor by the laboratory;
4. Patients should get counseling on the advantages and disadvantages of ES/GS, their limits, the possible impacts on relatives, and testing options;
5. ES/GS are not suggested for the age below 18, with these exceptions: a. Phenotype-driven clinical detection purposes; b. Situations where early identification or treatments are accessible and efficient; or c. Research that has received institutional review board approval;
6. A clear distinction should be established between clinical and research-based screening during the pretest counseling;
7. Participants should be told if individual IFs may be shared with databases and should have the option to opt out of these disclosures;
8. Patients should be alerted of protocols governing the re-contact of referral physicians as additional information regarding the significance of specific findings becomes available [2].

Previous findings indicated that, although subjects respected the care taken with ES/GS consent, they felt the procedure was lengthy and, for instance, the research required a 2–3 h consent in a tough process [6]. According to Bergner et al., compared to the general population, people with genetic diseases and their families are more tolerant of the dangers related to taking part in ES/GS research. This tolerance seems to be correlated with the following factors:

1. An increased likelihood of advantage for them, their family, or the community affected by their diseases;
2. Self-assurance in their capacity to cope with IFs;
3. A reduced assessment of the individual risk of research results given their current medical condition.

A consent form that considers the risks and benefits of the study in the framework of earlier experiences with genetic study and genetic disease might be beneficial to families dealing with hereditary disease [7]. The possibility of giving consent is considerably higher in diagnostic exome sequencing (DES) patients under the age of 18, suggesting that the health state may be a factor affecting the decision to choose for disclosure [8]. Sapp et al., interviewed 25 parents of 13 young probands with a range of uncommon genetic disorders in semi-structured interviews. The parents of affected children were often interested in learning more data about SFs related to their child's health-threatening reports [9].

"Dutch clinical geneticists often discuss topics such as the nature and purpose of the examination, as well as potential outcomes." (including IFs and variants of uncertain significance (VUS)), and the implications of the findings for the patient and their relatives during informed consent debates about GS [10]. Some practitioners use a layered approach to obtain informed consent, concen-

trating first on delivering vital data, then tailoring subsequent disclosure to the requirements of the particular patient, and verifying that vital data is presented in an obvious and intelligible manner. Layering information is an effective method since it concentrates on supplying a brief and straightforward general description at the very beginning. Additional topics can be covered as well, according to the patient's circumstances and informative requirements. Layered consent enables healthcare professionals to deliver adequate pretest consultation and informed consent protocols even in conventional environments or when time is limited [10].

3.1.2. Controversial Reports on the Genetic Variant

In a study conducted by Murrell et al, they analyzed 700 pediatric cases at the Children's Hospital of Philadelphia. Among the 576 subjects (82%) who were obtained for reporting ACMG SFs, 18 (3.1%) contained identifiable (pathogenic or likely pathogenic) variants. In their investigation, the most prevalent SFs were for hereditary cancer syndromes including BRCA1, APC, BRCA2, TP53, SDHB, and WT1 (38.9%), followed by cardiomyopathies (16.7%), and long-QT/Brugada syndrome (16.7%) including GLA, KCNQ1, MYL2, MYBPC3, and SCN5A. There was a diagnostic approach in 7 of these 18 individuals (38.9%). 28% of patients with SF also had a parent with SF. The paternal origin of the identified variant was not provided for 50% of the subjects with an SF [11].

3.1.3. The Penetrance of IFs/SFs Variants

In the first issue, the ACMG guidelines defined that variants with higher penetrance must be reported, however, the definition of "higher" were left to the clinical laboratories. Lawrence et al discovered a TP53 variant with up to about 10% penetrance for pediatric adrenocortical carcinoma and programmed for newborn screenings in Brazil which demonstrated the beneficial effects on mortality and morbidity in the carriers of this mutation [12,13]. The association of TP53 with Li-Fraumeni syndrome could not answer this reporting issue since this variation has not been correlated with Li-Fraumeni syndrome [14]. Variants with greater medical penetrance have to be taken into account and must be reported. However, reporting can be challenging to code bioinformatically, requiring human interpretation and probably medical consultations.

3.1.4. Lack of Functional Studies

Numerous case reports are published rapidly, often without conducting the functional evaluations necessary to support and elevate novel secondary findings (SFs) to clinically actionable levels. These reports need multiple records from all over the world with precise descriptions of the manifestations resulting from the mutation to be considered in the SF panel. Noteworthy, the new mutations which indicate new genes not included in the ACMG SF or other well-known guidelines lists, need deeper investigations both clinically and molecularly. To get through access to these novel SF variants, both the working groups and laboratories can follow the updates of well-known databases such as ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), VarSome (https://varsome.com/), and Franklin (https://franklin.genoox.com/clinical-db/home).

3.1.5. True Positive versus False Positive IFs/SFs

In all scenarios, SFs should be developed according to confidence degree considering their deleteriousness, by a conservative method indicating a minimum of evidence-supporting pathogenicity of the variants. The extent to which a disease and gene have been examined is another consideration in calculating the rate of reportable SFs. More specifically, the more people who have been diagnosed with a medical condition and examined for gene mutations, the more disease-causing variants will probably be detected [14], filling the gaps occurring between computational predictions and functional studies.

3.1.6. Costs

IFs/SFs can impose extra burdens in different dimensions. The impact of the added financial issues for implementing searching for IFs/SFs in healthcare settings should not be ignored. The findings indicated that extra expenses, such as the length of time required for pre-test data, post-test data, specialized medical appointments, and genetic counseling for at-risk families, would be required in individuals with positive findings [15].

4. Solutions

Considering the reviewed publications with various standpoints and problem-solving suggestions, the fundamental and critical items are listed and summarized below. These suggested solutions include: Laboratories, physicians, and genetic counselor decisions; Collaborations between professionals; Somatic or germline reports; Cancer versus non-cancer statuses; Pharmacogenomics approaches; Actionable SFs; updates of the guidelines; Function of the variant (nonsynonymous/frameshift/splicing/stop-gain/stop-loss, etc.); Bioinformatics and datasets; Clinical characteristics of patients including age, gender, having disease-phenotypes or without identifiable manifestations (healthy); Patient education and personalized

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opt-in decisions; Population ethnicities and backgrounds (population stratifications); and finally, Cost-effective and financial issues (Figure 1).

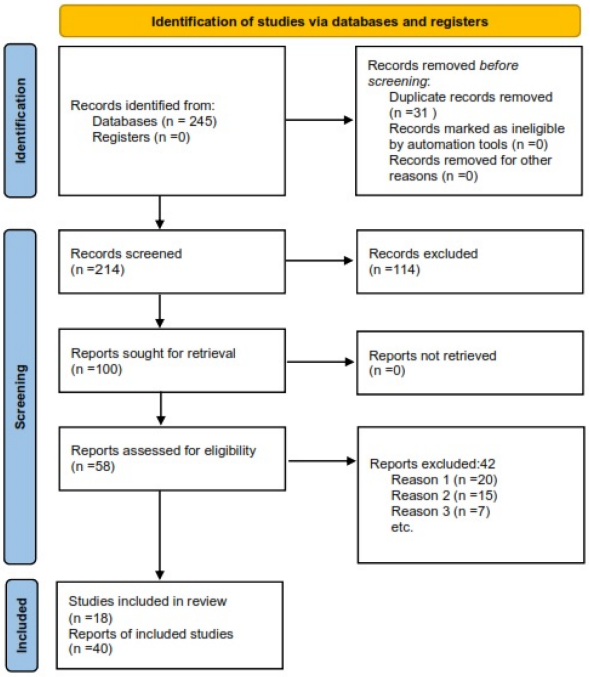

Figure 1: PRISMA diagram of the whole process of including and excluding the studies focusing on the Incidental findings (IF's) or Secondary findings (SFs) of genome or exome sequencing results. The reason I refers to the studies which reported only the IF's or SF's as their additional reports and not main concentrations. Reason 2 reflects the studies which mentioned IF's or SF's after Pathogenic, likely pathogenic, and Variant of Uncertain Significance (VUS) variants as their analysis strategies. Reason 3 excluded the studies which had the secondary but not related to the findings (secondary findings).

4.1. Laboratories, Physicians, and Genetic Counselors' Decisions

The term IFs has been explicitly substituted with SFs, reflecting a desire for labs to diligently search for such kinds of variants throughout the process of clinical examination (as opposed to accidentally discarding these variants during reviewing the sequencing data). Yet, well-known guidelines such as ACMG have been updated allowing patients to opt out of obtaining these kinds of outcomes [16].

While some laboratories have decided to closely follow the recommendations, other clinical laboratories have made their decision to include additional genes, beyond those suggested in the recommendations, in their SF analyses. However, other laboratories have even made the decision not to continue searching for these variants and instead decided to keep the true IFs. As a result, physicians who desire to request ES/GS should be informed that IFs/SFs can be seen on the report if a patient opts to receive them, and they should carefully review the consent form of the offering laboratory to learn their particular method for SF reports. The majority of the suggested genes involve autosomal dominant cancer predisposition syndromes (such as the BRCA1 and BRCA2 genes; for instance, a patient carrying a pathogenic SF variant reported in the BRCA1 gene might require a referral to an oncologist [17].

Laboratories suggest a diversity of other SF panels containing carrier conditions for autosomal recessive statuses and pharmacogenetic variants. Most laboratories report findings to patients without any age limitations. This is usually in contrast with laboratory guidelines governing Huntington disease prediction testing of children. Some laboratories do not clarify what, if any, secondary findings (SFs) can be shared with other relatives who have been tested. Laboratories may intend to follow the recommendations but have yet to determine the cost of this updated test or finalize the revision and approval of the informed consent documentation. Patients and their healthcare professionals may be affected by differences in laboratory standards. It allows individuals to opt for a laboratory depending on their preferences for the return of IFs, subject to limitations like insurance coverage. As a result, laboratory employment might indicate consumer preferences within policies. The marketplace might play a role in the formulation of policy in this field as well [18]. Even if one agrees that labs should proactively investigate for particular genetic variants and supply the clinician with the findings, it does not seem evident that a clinician should be unable to act as a gatekeeper for the data that the patient is permitted to receive, so long as the patient is clear in his/her rejection of additional data during the complicated procedure of determining the significance of this genetic details.

It almost seems enforced to state that "patients have the choice to refuse clinical sequencing if they consider the risks of potential IF identification exceeds the advantages of screening." [4]. It contends that patients should be supplied life-saving sequencing for a condition they already possess only if they are prepared to embrace additional, possibly life-threatening genetic testing data for a condition they may develop in the future, irrespective of whether they consider the extra data desirable [19]. The issue of patients rejecting all IFs is not addressed either, avoiding the lab the cost of pursuing them and any challenges in deciding which findings to report. This 'one size fits all' strategy to consent also ignores noticed gaps in the demand for genetic details among social and ethnic backgrounds [20,21].

Most physicians would likely agree that the diseases listed in the guidelines are significant and, to varying degrees, actionable. Early warning of these potential conditions can provide crucial guidance for future management. The majority of patients or parents prefer that their physician inform them of vital, perhaps fatal diseases for which they might be at risk. Yet, the recommendations seem to imply that everyone undergoing ES/GS should be routinely checked for a growing number of genetic disorders, even beyond focused testing or true IFs. Since there is no indication that people who perform ES/GS are at a higher risk of the listed disorders than the general population, the inference may be that we should undertake population-based tests for significant clinical conditions.

Meanwhile, the Working Group argues that, while the expense of further testing, lab time, interpretation, and reporting will be feasible, it will be too challenging to respect patient requests for more investigation while obtaining findings. This appears to be both doubtful and troublesome. According to reports, a wider social and professional discussion is needed to determine if we - as test providers, physicians, and patients - are truly prepared for mandated genetic screenings [3]. It should be emphasized that, when trying to get informed consent, consultations for informing patients about the consequences of SFs/IFs should be separate from medical advice and supervised by a genetic counselor. Guidelines that will direct the incorporation of genomics into the clinical setting have been considered, and they take into consideration the fact that expanding exome analyses will lead to IFs/SFs which will modify medical geneticists' option of practice [22].

According to Amendola's study, the first biologist may have spent up to 37 minutes reviewing the literature and categorizing every variant resulting in HGMD disease. For double-reviewed variants, 53% of classifications were incorrect, highlighting the need for a properly monitored variant interpreting database [23]. Thauvin-Robinet et al.'s team spent 6.3 minutes per patient on genes indicating a predisposition to a condition in childhood or adulthood and are amenable to prevention or treatments, and 1.3 minutes per patient on genes during genetic counseling. Nevertheless, a mean of 37 extra minutes per variant was necessary for the few variants which need to be reinterpreted. This finding should be interpreted with caution while the time spent might be influenced by the biologist's degree of knowledge and interest [15].

4.2. Collaborations between Professionals

A strong collaboration between the medical molecular geneticist and the clinical geneticist appears to be required to specify the analytical strategy to which a patient has consented. Additionally, additional experimental (follow-up) research on the utilization of ES in testing, as well as patients' awareness and decision-making, are required to provide clear criteria for the informed consent processes. More ES experience may educate us regarding the frequency of SFs, which is vital data for patients in the stages of making decisions [24]. However, in the era of patient-centered medicine, a shared decision-making model has emerged, advocating that patients and medical professionals exchange information and perspectives before arriving at a decision. [25,26].

4.3. Somatic or Germ-Line Reports

Gray et al investigated the use of matched somatic and germline WES in a comprehensive cancer center. They discovered that while most oncologists have extensive experience regarding the use and interpretation of somatic genomic tests, they have minimal familiarity with germline tests. However, the respondents decided to disclose most WES findings from both somatic and germline testing rather than the patients. Oncologists were also concerned about interpreting data, sharing non-cancer findings, and trying to determine the "actionability" of variants. It has also been discovered that individuals suffering from advanced lung and colorectal cancers have positive views toward getting a genetic test but have somewhat low levels of genetic information and that many of them desire to learn all WES outcomes. Gray et al.'s findings improved the area by indicating that, while physicians anticipate numerous challenges in providing care including large-scale sequencing, patients with incurable cancers declare an overwhelming need to learn about genomic results, regardless of whether they are relevant to their immediate medical treatment [27].

When asked about the somatic genomic examination, the majority of oncologists expressed moderate to high confidence in their skill to understand somatic findings in their disease field, clarify somatic genomic principles to patients, make suggestions for therapy using somatic genomic data, and pinpoint proper consultants. The elevated level of confidence could be attributed to the truth that the oncologists in Benson et al's and the National Comprehensive Cancer Network (NCCN) studies ordered and interpreted numerous somatic tests, as well as the truth that lung and colorectal adenocarcinoma are malignancies for which genomic analysis is part of guideline-based cancer treatment [28,29]. Nonetheless, oncologists predicted several difficulties in providing somatic WES treatment, such as coping with and analyzing huge amounts of data and establishing the actionability of

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somatic results [30]. Several oncologists stated concerns about determining how much somatic data to communicate with patients and managing patients' expectations. Furthermore, oncologists raised worries about their capacity to stay current with the literature in this fast-changing profession [27]. If there was an authorized targeted treatment for another cancer kind or a clinical trial was accessible, all respondents intended to share somatic results.

Oncologists' eagerness to investigate new treatment options and encourage registration in clinical trials was linked to liberal attitudes about somatic disclosure. Abundant physicians have also suggested that patients have a "right to be informed" about their somatic data [31,32]. Many oncologists stated that they would be less ready to reveal data if it did not have an impact on cancer care or prevention and that the "actionability" of the results would be a key consideration of disclosure. Some oncologists stated that they might not reveal the patient's germline data if they did not already have children or intended to have children in the future. An individual might speculate that in cases of advanced cancer, when the therapeutic utility of germline information for patients may be more obvious, physicians' and patients' risk-benefit calculations as they balance the importance of germline data and disclosure may differ significantly from those in other contexts. Several oncologists also mentioned a wish to share germline data with a genetic counselor or another clinician. Organizations that offer WES or WGS might require to make pertinent clinical and counseling skills accessible to oncologists, patients, and relatives of patients due to the intricacy of the information and the familial implications of germline findings [27].

4.4. Cancer versus Non-Cancer Individuals

Since cancer is frequently driven by genetic alterations, oncology is an excellent context to investigate clinical sequencing. Targeted germline (typical tissue) and somatic (tumor) DNA sequencing have drastically developed results in selecting high-risk and cancer-affected subpopulations, and larger gene panels are being employed in practice [33–42]. Whenever somatic and germline DNA are analyzed simultaneously, the power of sequencing rises because paired sequencing differentiates between somatic and germline changes and can reveal previously unknown hereditary cancer risks [43–45].

Oncologists have some knowledge of ordering and interpreting germline genomic testing linked to cancer, but they have little experience requesting and interpreting tests irrelevant to cancer [46]. One of the most important oncology concerns is how to effectively help cancer clinicians as they merge enormous amounts of genetic information into daily cancer care. Supporting providers must begin with attempts to increase the accuracy of data in referenced genomic databases, and attempts to optimize bioinformatics methods and assets for variant calling and interpretation. Advanced methods of medical education and decision support will also be required in such case. Given the quick change in genetic variant data, dynamic genomic analyses and point-of-care medical assistance can help healthcare providers in understanding the possible consequences of somatic and germline variations and better personalizing recommendations. Physicians may receive support via programs created by their regional institutions in addition to institutional interventions. For instance, several organizations, such as the Dana-Farber Cancer Institute (DFCI), have created multidisciplinary "Genomic Tumor Boards" where healthcare professionals can talk about patients in a case-based form, emphasizing their genomic or proteomic information to receive feedback or input from peers with knowledge in molecular biology, clinical oncology, pathology, clinical trials, and clinical ethics [44,47].

Most patients' overwhelming desire for the return of both types of somatic and germline genomic data, along with their generally minimal understanding of genetic knowledge, implies that patients will also require aid in comprehending and making well-informed choices regarding genomic testing. At the time of initial consent and sample collection, educational tools and decision support will be essential to ensure that patients can make informed choices about the types of findings they wish to receive. Patients who performed cancer-related ES/GS will need to know some basic genetic principles such as the distinction between somatic and germline examination, the fact that males can transmit germline mutations onto their offspring, and the fact that not all germline mutation carriers are susceptible to disease. Computer-based learning treatments have been proven to increase awareness in the context of germline cancer genetic counseling and might be useful in this type of setting [48].

Furthermore, as physicians do not frequently ask about patients' choices for the return of particular outcomes while ordering laboratory testing, further research is needed to establish how to better detect and respect patients' sequencing requests. Another possible option is to include patients' sequencing choices on the test request, permitting the laboratory to personalize result reporting. Lastly, resources will be required when the findings are returned to avoid misunderstanding and guarantee the actions taken by patients and relatives are evidence-based and compatible with their opinions. Given the rapid adoption of genomic testing in oncology, the creation of these

resources for patients and families is of the utmost importance [49,50]. Conclusively, patients with significant solid tumors indicate a significant desire for receiving genetic data, particularly IFs. However, these choices may not be founded on a thorough understanding of genetics or the consequences of results for the health and medical care of patients or relatives. Additionally, oncologists who deal with these patients are concerned about their capacity to evaluate, communicate, and make choices about the wide range of somatic results produced by WES, as well as their capability to manage the germline results that may deduce from parallel sequencing. Resources to help patients and healthcare professionals address these issues are a top focus for the cancer community [27].

4.5. Pharmacogenomics Approaches

Secondary findings obtained from pharmacogenomics testing are in the category of IFs. WES data may quickly determine genes that are easily examined by next-generation sequencing (NGS) technology (such as CYP2C9) with a large number of significant variations in the coding region. Conventional WES, on the other hand, does not perform well for genes including CYP2D6, making it difficult to obtain highly reliable and relevant information [51,52]. Due to technological complications, pharmacogenomics testing may be restricted, which might result in an incomplete profile and reduce the therapeutic value of detailed testing. This is especially imperative for drugs that are processed by many pharmacogenetic enzymes [53]. It is challenging that the background of Pharmacogenomics findings provided during clinical WES testing differs from that of solely Pharmacogenomics testing. The Pharmacogenomics results in a WES test are secondary to the variations found in disease-causing genes, which may be responsible for the patient's symptoms and may go undetected. It is already challenging to explain the variants associated with the initial genetic problem to patients, making it even more difficult to appropriately emphasize secondary findings (SFs).

Additionally, the physician ordering the WES test might not be the one who prescribed the patient's drugs, which adds another level of complication to the treatment and efficient utilization of the Pharmacogenomics findings. WES test findings are frequently obtained as static, scanned files, consequently, there is a critical need for integrating this information into an electronic system that can notify prescription to medical professionals of important Pharmacogenomics findings. Therefore, Pharmacogenomics findings for diagnosing Odyssey patients might not be considered in their present or future medications prescription [53]. The effective utilization and accessibility of Pharmacogenomics findings are delayed by clinical and technological issues.

Clinical decision support (CDS) systems, which include automatic alerts to notify prescribing doctors of relevant gene-drug interactions detected for a patient, have been implemented with educational components to help clinicians understand these notifications. [54–59]. However, there are still challenges in the way of a successful and effective combination of Pharmacogenomics data even with these technologies. The clinical findings for the patients are commonly pdf files created by a third-party company and scanned into the patient's electronic medical records (EMR), which prevents the Pharmacogenomics CDS system at the institution from issuing alerts based on the results. For each patient having Pharmacogenomics results, a pharmaceutical consultation needs to be carried out to make sure the prescribing doctors have access to the information. Institutions may be significantly exposed to risk and responsibility for patient neglect if they will not take additional measures to emphasize these SFs in the medical record [53].

ES results may be used to generate decision support warnings using Pharmacogenomics IFs, which offers promising possibilities for the development of proactive Pharmacogenomics management in the future. The suggestions offered by Nishimura et al. to those creating decision supports for ES are as follows: understanding the limitations of the institution lab results of electronic health record (EHR) systems in managing genomic information; budgeting for the time necessary to personalize variant-drug risks to the clinical setting in which they are expected to happen; and, ultimately, allocating enough resources to continuously gather, synthesize, and apply Pharmacogenomics evidence.

The integration of the Pharmacogenomics IFs from ES into current clinical processes may be greatly enhanced by the use of EHRs and the decision assistance resources that go along with it. Nishimura et al developed a demonstration of the concept for IF-based warnings and investigated technological difficulties, problems integrating workflows, and difficulties with content creation. ES decision support systems may currently be delayed by technical and physical issues at many institutions, but it is predicted that as EHR systems advance and are centralized, Pharmacogenomics databases expand, and this technology will soon become a promising one [60]. The economic effects of returning ACMG-recommended IFs/SFs to patients getting GS were assessed in intriguing research using a quantitative methodology [61]. The authors found that returning IFs/SFs is economical for some patient populations but not for overall healthy people unless NGS costs lower than $500. In this series, the evaluation of pharmacogenetic

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variants or combinations of variants proved the limit of ES for reliable pharmacogenetic counseling.

As it is discovered that only 61% of the high-priority Variants (Pharm GKB 1A/1B categories) and multi-allelic combinations are common, interpreting the risk while prescribing medicine was occasionally problematic. To address this issue, the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP) evaluated the frequency and therapeutic accuracy of pharmacogenetic IFs/SFs annotated in the Pharmacogenomics Knowledgebase (PharmGKB) sequence variations or combinations of variants in a cohort of 1101 persons using SNP chip analysis in addition to ES. Surprisingly, individuals' prescription data were utilized to identify individuals who received prescription drugs despite having a genetic mutation that might affect effectiveness. Nineteen PharmGKB 1A/1B variants or variant combinations were detected in SNP chip sequence data, and 21 PharmGKB 1A/1B variants or variant combinations were detected in ES data utilizing the TruSeq kit (Illumina). Only 9 subjects exhibited pharmacogenetic IFs/SFs connected with decreased drug effectiveness, showing that some pharmacogenetic IFs may be beneficial for directing treatment and should be reported [62]. However, another research of 159 Mayo Clinic doctors found that half of them were worried about including pharmacogenomics data in primary care. It emphasized the need of raising healthcare practitioners' knowledge of such advancements [59]. The prevalence of the pharmGKB pharmacogenetic alleles discovered in this work were not surprising, as Parsons et al. discovered a median of a single pharmGKB SNP per CES, albeit with a substantially reduced list of SNPs [63]. The question of prospectively interrogating pharmacogenetic variations associated with a particular drug rather than providing a list of pharmacogenetic variants or the combination of variants in the ES/GS report stays unresolved, particularly given that the physicians must learn how to handle pharmacogenetic findings [62]. The implementation of GS in the future should solve this problem given the limitations of pharmacogenomics expectations from ES. The significant majority of these variants also have dose-dependent recommendations that are now reserved for adults, which might restrict their usefulness in children with neurodevelopmental problems [15].

4.6. Actionable SFs

Nuclear DNA genes approved by the ACMG and other genomic contents (such as mitochondrial DNA), as recently disclosed, were among the IFs that were identified as being medically actionable [4,64]. Adults are considered to have "actionable" genes if they have deleterious mutations that would lead to specific, well-defined medical recommendations, reducing mortality or significantly reducing morbidity. Any concerns prompted by an unanticipated propensity to disease have to be outweighed by the intervention's benefits. A list of "bin 1" genes, existing clinical testing for genetic abnormalities, and genes suggested by group members based on their clinical competence will be all taken into account when actionable genes are determined to be placed on the IF gene list [65]. The working group identified genes that were unanimously agreed upon as justifying reporting when a known harmful mutation is detected. According to their areas of interest or expertise, group members were listed genes that had ambiguous disease associations, for which related disease screening and/or therapy had questionable benefits, or for which additional information was needed to make a decision. The committee continually expands and updates this list as new information about the relationship between genes and diseases, or their actionability, becomes available. Particularly, a database of actionable variants for adults is created, therefore diseases that might go untreated in adults are only included. The effect on reproductive decision-making (such as reporting carrier status) is excluded [66]. Actionability is defined differently by different groups, but it often involves the availability of treatment and prevention. Others have approved or brought up problems like the capacity to plan or modify lifestyle choices or affect reproductive decisions [67–69]. Some of the patients in Parsons et al's study was diagnosed incidentally with the MELAS mitochondrial disorder (mitochondrial encephalomyopathy, stroke-like episodes lactic, and acidosis) [63].

4.7. Latest Update of the Guidelines

The recommendations from the ACMG for disclosing IFs in CES and genome sequencing were published in March 2013. These recommendations state that all testing laboratories, regardless of patient preference or age, should notify the ordering clinician of any pathogenic mutations discovered in any of the 56 specified genes related to 24 diseases [4]. The clinician should "contextualize these findings to the clinical circumstances (e.g., ...patient preferences, etc.) and the provider and patient will participate in a shared decision-making process regarding the return of results" [70]. The ACMG targeted these circumstances due to their actionability; the morbidity and/or mortality of the related disease might be lessened via primary testing and treatment [4].

The ACMG updated its recommendations, which indicate that when patients underwent ES/GS, they "should have the choice to opt out of the analysis of medically ac-

tionable genes." The continuing debate over IFs in WES and a survey of ACMG members, according to reports, led to the ACMG's conclusion to update these recommendations [71]. In the 2014 version, SFs would be notified only if patients completed an informed consent document. The 2017 version, on the other hand, contains a choice to opt out of getting SFs. The European Society of Human Genetics (ESHG) made particular suggestions according to factors including the risk-benefit balancing, testing costs, the accessibility of preventive and therapeutic measures, patient autonomy, the psychological and clinical impact, and inequalities in acquiring health services [72]. As diagnostic laboratories are not required to follow these standards, the detection of such SFs may differ per population. SFs are only documented in genes related to processable diseases, including cystic fibrosis, or in allele carriers in autosomal recessive conditions with a frequency of more than 1/125 in Alvarez-Mora et al.,'s study [73]. The ACMG recommendations were revised between 2016 and 2021, with the most recent revision from 2022 (v.3.0) listing 78 genes and adding 5 new genes in comparison with 2021 [74,75]. The working group has recently declared that they will update the list every year [75].

Based on factors including the risk-benefit ratio, screening expenses, the accessibility of therapeutic and preventive measures, adherence to the concept of patient autonomy, the psychological and physiological effects, and disparities affecting the availability of healthcare facilities, the European Society of Human Genetics (ESHG) made some specific suggestions [72]. Along with ACMG and ESHG, some other professional genetics communities and networks, including the eMERGE Network and the French Society of Predictive and Personalized Medicine, have declared that "actionable" secondary genetic findings should or could be disclosed (French Agency of Biomedicine, n.d.) [76]. The ACMG project also sparked an in-depth debate that concentrated beyond detecting testing and SFs to return, in addition to the ACMG list, other potentially "actionable" genetic information from biobank donors and study participants. This discussion also included the financial benefits of disclosing such variants [77–79].

4.8. The Function of the Variant (nonsynonymous/frameshift/splicing/stop-gain/stop-loss, etc.)

In a pediatric-based WES test investigation, Headrick et al discovered that accidentally identified VUSs in genes correlated with arrhythmogenic right ventricular cardiomyopathy (ARVC) showed striking parallels with background genetic variation in healthy individuals. IFs in children lacking clinical signs of cardiomyopathy or ARVC are not expected to be indicators of a monogenic disorder. The regions of common pathogenic relevance for altered proteins can be refined by further investigation of genetics Amino acid-level signal-to-noise analysis in large-scale population studies, which also enables the analysis of ultra-rare variants. One approach for differently weighing the diagnostic importance of an accidental variant is gene and amino acid level investigation of the variant in issue, normalized versus uncommon genetic variant frequency at the loci of interest [80].

Due to incomplete data in some populations and the diversity of interpretation techniques, calculations of the global frequency of IFs should be used with care. The calculation of the frequency of IFs in all evaluated publications was according to the frequency of pathogenic and likely pathogenic variations in the analyzed cohort, but the proportion of patients who carried the related diseases who carried the variant The frequency of the pathogenic and potentially pathogenic variations in the analyzed cohort was used in all evaluated publications to estimate the frequency of IFs, but the proportion of patients with the linked illness carrying the variant was not disclosed. In addition, 90% of the publications that were analyzed indicated IF rates in their investigated cohorts between 0.5% and 6.5%, while two studies indicated a frequency of IFs over 12% [81,82]. The greater frequency may be addressed partially via the application of alternative gene lists to return the IFs; for example, some research decided to incorporate a better comprehensive list of genes containing actionable variants [23,66,81,83–85]. From September 2020 to November 2021, Zhu et al. conducted a prospective analysis of 90 continuing pregnancies with ultrasonography abnormalities that underwent trio-based pES after obtaining normal CNV-seq data in a single location in China. The underlying genetic causes of anomalies in fetal development, unsolicited fetal findings, and parental carrier statuses were identified using panel-based exome sequencing (pES), which includes exome coding and splicing regions as well as the mitochondrial genome, for both fetuses and parents. At last, they suggested that trio-based pES could provide extra genetic details for pregnancies having fetal ultrasonography defects but no CNV-seq detection. The IFs and parental carrier status revealed using trio-based pES combining splice-site and mitochondrial genome sequencing broadens its medicinal applications, although careful genetic counseling is required [86].

4.9. Bioinformatics and Datasets

Bioinformatics users now have a much easier time interpreting WES variations due to advances in software tools

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and database references. Contrarily, the release of guidelines and standards in the USA, Canada, and Europe has split the conversation around the difficulty of identifying, categorizing, and disclosing IF [87,88]. Additionally, the application of anonymous data by the study, which suggests that patients were not informed of the findings, may have obliged the researchers to underestimate the significance of consulting a referent lab for accurate interpretation. It is debatable whether or not to use the ClinVar categorization of a variation as a first filter and to review variants with different interpretations. The worldwide community is making a lot of effort to evaluate the medically relevant variations in variant categorization, which should enhance this method going forward and the treatment of individuals with or at risk for genetic diseases [89–91].

4.10. Clinical Characteristics of Patients

Patients' characteristics including age, gender, having disease phenotypes, or being healthy without identifiable manifestations should be considered as well. In their systematic review of Frequency and management of medically actionable incidental findings from genome and ES data, Elfatih et al pointed to the important issues mandating consideration. They included 20 articles with over 75 thousand subjects evaluating IFs in cohorts on healthy individuals (n = 5), on both healthy and disease (n = 5), and disease (n = 10) from different ancestries mostly from European, African American, and Asian descent and two in the Arabic people. The frequency of IFs was between 0.9-12.64% in different reports based on the frequency of the pathogenic and likely pathogenic variants [92]. All but one [93] were adults. Since many of the practical diseases associated with the genes listed in the ACMG guidelines manifest in adulthood, it is likely that adults—who are often referred for exome sequencing (ES) family testing (trio)—would prefer to receive secondary findings (SFs) for themselves rather than for their children. This was found in some but not all nations, and the variations were often minimal [94].

The technique of providing SFs has a significant impact on individual health but a negligible impact on population health since only a very small portion of the population gets referred for WES. However, there is increased interest in disseminating genetic findings to significant portions of the general population as part of biobank investigations and in establishing strategies for doing so [5,95]. Most European Biobanks declare that based on their national law, they are permitted to contact the study group to advise about findings concerning their healthcare condition [96]. Of the 115 trios analyzed by Talati, about 36% were obtained from trio-ES, and 31% of the results might help define the fetal phenotype. They revealed that women obtaining trio-ES results had higher anxiety, indicating the possible desire for additional assistance or counseling to influence present and future reproductive decisions [97]. While the debate over the advantages and disadvantages of such testing continues, very little evidence is available regarding patients' perspectives on SFs, particularly those that may lead to differing perspectives, such as the patient's age, gender, or geographic origin. A few research, fortunately, focused on participant concerns; for example, Rini et al. analyzed participants' sociodemographic details [98].

4.11. Educating and Informing the Patients and Personalized opt-in Decisions

Many adolescents and their parents in the Warner-Lin et al. research anticipated informing about their risk for prevalent conditions such as cancer, Alzheimer's disease, and diabetes, ignoring the fact that informed consent meetings emphasized the low probability that WES would detect a clinically actionable SF. Adolescents particularly talked about being ready for disclosure sessions, asking how they could respond and what they can do to lessen the onset or severity [99]. A mistake in a center's policies may be that it prioritizes (the transferring of) data beyond psychological characteristics and aspects of family structures and the procedure for counseling [100]. The transfer of genetic information must consider the private principles and requirements of each individual engaged. Respect for the child's future autonomy is recognized as a primary reason in healthcare provider guidelines and ethical literature concerning the disclosure of IFs in pediatric WES [101]. Counseling ought to include a personalized explication of what has to be stated, including when, to whom, why, and how. Prior reports highlighted the importance of the ethical question about whether or not and how the issue of the child's future autonomy must be taken meticulously in genetic counseling (should counselors deal with the subject during counseling?) and clinical center disclosure guidelines (should all IFs be informed to parents?) [102].

Rini et al. performed a study in which 335 adults with suspected genetic problems who had diagnostic exome sequencing (DES) were randomly assigned to get both diagnostic findings only (DF; n = 171) and diagnostic findings in addition to education for extra genomic results and the option to ask for them (DF+EAF; n = 164). Examinations were conducted after enrollment (Time 1), after the receipt of diagnostic data, and—for DF+EAF—the education under examination (Time 2), and 3 and 6 months later (Times 3, 4). Their results demonstrated

that offering education about and an opportunity to learn about more findings that have weak medical actionability has few advantages and no negative effects [103]. According to Gereis et al.'s study, most of the parents stated having previous experiences with genetic tests and experienced some type of genetic counseling. The awareness of parents differed throughout the topics studied. Parents displayed a grasp of the different possible direct clinical advantages to their children performing ES/GS, as well as other genetic testing. The authors revealed that parents had a different awareness of the nature of prospective SFs, as well as problems with information security, confidentiality, and the use of sequencing findings independent of their child's medical care. Further, consultations with genetic counselors boosted comprehension significantly. Their findings suggest that ES/GS can be difficult for families to grasp, emphasizing the significance of training healthcare providers to investigate parents' comprehension of ES/GS and the consequences of testing on their children [104].

O'Daniel et al. released a survey of genomic sequencing testing interpretation and reporting methods in 21 United States laboratories in 2017. They claimed that all of the laboratories assessed provided SF reporting by the ACMG standards. They stated that only 4 of the 21 clinical labs in their sample needed SF opt-in, indicating intentional patient preference [5].

4.12. Population Ethnicities and Backgrounds (Population Stratifications)

There were differences in opt-in decisions to get SF findings across patients/families from various nations. As a result, 90% of patients and relatives in Romania picked the option of knowing their SFs, whilst those in Luxembourg did not. A possible reason for Romanian patients' overwhelming enthusiasm for receiving SFs reports might be the insurance coverage of the test. This may have resulted in a social prejudice not found in other European nations. In Finland, the experience in some University Hospital laboratories differed greatly from the findings on Finnish patients/families referred to BpG: about 80%–90% of patients referred to ES at some Finnish University Hospitals consent to receive SFs (Anttonen A-K, personal communication) [94].

The findings of Hitch et al. highlighted the relevance of researching various populations when considering the medical application of WES to properly and compassionately convey the potential consequences of this novel method and return outcomes [105]. It would be vital to disclose the IFs even to heterozygous people for AR disorders in groups that are defined by a high proportion of consanguineous marriages, such as the Arabic community, to detect relatives at risk [106–108].

4.13. Cost-Effectiveness and Financial Issues

Gallego et al in their study found that about 50% of publications mentioned the cost of WES and test coverage [109]. It includes a variety of sub-challenges throughout the WES data generating, processing, and interpretation approach. Several researchers from 2014 to 2015 believed that WES remains too expensive to be applied as a standard of treatment in various conditions such as acute myeloid leukemia, epilepsy, sudden unexplained death, axonopathies, and cardiac arrhythmia [110–114]. However sequencing prices have decreased dramatically in recent years, it is noteworthy that even in 2014, some experts believed that sequencing is excessively costly itself [115–118]. Other reasons given by the authors for the increased price of these tests are the expense of information storage, and necessary Sanger confirmation of WES findings [119,120]. Another factor is data interpretation when compared to more focused sequencing [119,121,122]. Beckmann et al. concentrated on the potential use of WES in newborn screening and conduct a more detailed cost analysis that directed them to the opinion that from a financial standpoint, generalization of this method with present practices would require an enormous effort that is likely to jeopardize the social healthcare schedules. These important economic, social, and human costs are associated with the longer time professionals need for explaining and informing patients and families about WES findings [123,124].

Only when Whole Exome Sequencing (WES) is fully integrated as a standard treatment for certain diseases within the medical system will it be feasible to implement it widely in clinical practice. This requires a thorough economic assessment of potential funding sources and reimbursement schemes for this type of investigation. Numerous publications from the USA, UK, and Germany that were published after 2014 claimed that economic assessment and cost calculation studies must still be carried out to properly prove the relative cost-effectiveness of WES in comparison to other methodologies [125–131]. The requirement for insurance companies to cover these tests was cited as one of the major barriers to the wider clinical use of WES, particularly in the United States [131–135].

Demonstrating the clinical efficacy and cost-effectiveness of these tests is essential. Additionally, insurance providers and the public health system must develop the administrative infrastructure needed to fund these tests, including the creation of new billing codes [132,

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136,137]. The reduction in time to identification and the price of other tests demonstrates the cost-effectiveness of WES tests, and in some circumstances, WES might be recommended as first-line testing [138]. The Working Group's subsequent claim that following patient wishes would be unwieldy is unconvincing, especially in light of the higher expenses associated with giving IFs. The proposals create a false dichotomy between genetic libertarians, who support for complete return of all genetic data, and genetic empiricists, who argue against releasing IFs since their relevance is unknown. This conflict ignores the significant work carried out in the center ground of layered consent and patient-centered return of findings [139–141].

5. Discussion

The present review comprehensively investigated the publications which focused first on the SFs in the clinical context and secondly, on the ethical approach resulting from the process of finding this information to report them to the patients. However, there have been some standards in the SFs recommendations such as updating ACMG versions, but there are multiple evidences representing that there is an increasing tendency of professionals to report and patients to receive them. This review categorized the advantages and disadvantages into two major categories and some sub-categorizations. Concerns and solutions as the main areas of focus were discussed via these subgroups; for concerns: modernizing the opt-in informed consents, controversial reports, lacking functional evaluations of novel variant reporting, penetrance of SFs, true positive versus false positive SFs, and costs; for solutions: professionals' decisions and collaborations, patient's preferences and personalized opt-in options, somatic or germ line reports, cancer versus non-cancer cases, pharmacogenomics approaches, actionable SFs, guidelines updates, variants functionality, bioinformatics and datasets, clinical characteristics of patients, population ethnicities and backgrounds, and cost-effectiveness and financial issues.

There are some important points in the tendencies all over the world facing the IFs/SFs. These points are generally related to the positive trend of both professionals and individuals to inform and to be informed about the IFs/SFs, respectively. In recent years, several studies have addressed the issue that guidelines such as ACMG and ESHG could not cover all aspects of IFs/SFs both ethically and medically. The main focuses of these studies (reviews, case reports, and original articles) have been the modernized opt-in informed consents according to some items including prenatal/post-natal or pediatric/adulthood, actionable variants, cancer/ not cancer situations, population-based backgrounds or different ethnicities, time- and cost-effectiveness, the education level of subjects and clinicians, and the combinations of pharmacogenomics findings to introduce medicinal treatments and personalized prescriptions leading to a healthier lifestyle.

Interestingly, the reports during two recent years (2022–2023) represent the importance of prenatal IFs/SFs and the more pharmacogenomics-based data having actionability impacts. Concerns about the ethical approaches to secondary findings (SFs) persist; however, the current review presents notable solutions that are both ethically sound and practically feasible. These solutions have the potential to be adapted for different populations, considering various psychosocial, educational, and cultural factors. Results also found that recent reports are concentrated on the high-volume WES tests of subjects from biobanks and healthcare centers. The populations which were studied in large-scale subjects were Turkish, Japanese, Italian, American, Chinese, South African, and Dutch [10,142–147].

6. Conclusions

In conclusion, while concerns about the ethical issues in reporting secondary findings (SFs) persist, this study has introduced notable solutions that are both ethically sound and practically feasible for implementation. This review also found that recent reports are focused on the high-volume ES tests of subjects from biobanks and healthcare centers. There are notable suggestions that need to be considered both by the updates of guidelines and professionals. These suggestions include the combination of pharmacogenomics approaches regarding population backgrounds to build ethnicity-based panels of SFs. This will lead to a more suitable time- and cost-effective management of SFs reporting in higher layered information. With a wider collaboration between professionals (medical geneticists, molecular geneticists, physicians, and lab experts), a more efficient network will be organized that can aware and educate the patients about their SFs rapidly and accurately.

Author Contributions

F.T. performed data accumulation, analysis and manuscript preparation N.P. contributed in revision of manuscript, M.M.A. was involved in study concept and supervision, A.S.N.L. and A.G. were involved in manuscript preparation.

Availability of Data and Materials

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Consent for Publication

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Conflict of Interest

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