Molecular Autopsy: Integrating Discovery and Precision thorough Next Generation Sequencing with Emerging Prospects for the Future

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Abstract

Molecular autopsy has evolved as a crucial technique in forensics and identification of medical condition specifically in revealing the genetic architecture of sudden death where conventional autopsy results remain in definitive. With evolution in Genomic sequencing two significant methods NGS (next generation sequencing) as well as Sanger sequencing have majorly contributed to the field. It retains its utility for the confirmation of genetic differences, verifying results from Automated large scale processing systems and researching specific gene alteration accompanied by genetic disorders. Nevertheless, its confined as well as high cost per base makes it ineffective for extensive investigation. It validates comprehensive examination of whole genomes, assisting the detection of disease-causing genes connected to Cardiac channelopathies, Metabolism errors and various Congenital diseases often intertwined in SUD's (sudden unexplained death). Furthermore, standardizing databases and procedures is crucial to enhancing reliability and reproducibility across many labs. the incorporation of bioinformatics technologies and international collaboration are also key factors in improving the precision of variant interpretation. In the end, molecular autopsy will continue to develop as a revolutionary method in both forensic and clinical medicine thanks to the cooperation of sophisticated sequencing technology, through data analysis, and ethical consideration.

Key words – Sanger sequencing, Next generation sequencing, Forensic genetics, Molecular autopsy, sudden unexplained death, disorders of genes.

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1. Introduction

A molecular autopsy is the method of investigation of unexpected death also referred to as post- mortem genetic analysis. It is an essential tool to reveal the uncovering genetic cause of death in the cases of Sudden Unexplained Death (19). Molecular autopsy has become essential in forensic investigations of sudden deaths. Identifying genetic mutations linked to cardiac conditions, aiding both diagnosis and family risk assessment (43). Also identifies inherited arrhythmia syndromes and provides valuable insights into diagnosing arrhythmia-related fatalities (66, 73). Postmortem NGS expands testing capabilities, uncovering mutations even in degraded samples. Next-generation sequencing has become a crucial tool in uncovering genetic causes that may remain hidden in cases of sudden cardiac death which remains one of the leading medical concerns in sports cardiology (19, 56). It primarily focuses on examination of hereditary information from a deceased individual's biological samples. (71) Its foremost aim is to find an inherited component for demise when a traditional autopsy analysis is unable to unravel the cause of decease. Correct indication of molecular autopsy is considered a key issue as it is strategically for public health (14). Researchers used next-generation sequencing to examine a large set of genes in young individuals who died suddenly and were found to have structural problems in the heart (29). It is essential in the Sudden Cardiac Death (SCD) cases in youngsters, genetic disorders like Channelopathies as well as Cardiomyopathies are responsible. Samples collected while or after autopsy are utilized for post – mortem genetic analysis. Advanced molecular autopsies apply NGS (next generation sequencing) techniques to examine the immense quantity of genetic codes more rapidly and viably than conventional methods). Molecular autopsy integrates multiple genetic technologies, with Next-Generation Sequencing (NGS) at its core and Sanger sequencing serving as the confirmatory standard. Postmortem DNA can be extracted from fresh or formalin-fixed paraffin-embedded (FFPE) tissues, although the latter poses challenges of fragmentation and contamination (55). It enhances the graphs of Genotype and Phenotype equivalence. Furthermore, it assists in obstructive clinical care by recognizing at-risk members of the families there by combining medical utilization and forensic investigation. The ethical, legal, and social ramifications of molecular autopsy extend beyond the lab. Careful handling of genetic data interpretation is necessary to prevent variations from being misclassified and possible family anguish. It also permits the recognition of disease-causing mutations connected to several genetic disorders that can lead to unexpected death. By shedding light on genetic predisposition, molecular autopsy enriches the standard of investigation of death, contributing revelations into litigious disputes

2. History

Molecular autopsy is the post mortem examination carried out to reveal the cause of demise in the case of inexplicable deaths. Postmortem molecular analysis was suggested past two decades for the first time. It represents the procedure which concentrates on the usage of genetic assessment in autopsy samples with no definitive diagnosis. These molecular autopsies appear as accompaniment to conventional autopsies with the capability to recognize the genetic manipulation that may be liable to the pathology which prompted the SUD (sudden

unexplained death). Previously Sanger sequencing was utilized to examine the gene samples, but the advancement of NGS (Next generation sequencing) drastically raised the extent and cost – effectiveness of these examinations letting the entire exome and genetic sequencing. The use of NGS has improved the ability to detect inherited Cardiac disorders that often go unnoticed in standard autopsies (53). Presently this method is applied to reveal the genetic mutation which may explain the demise, assisting investigations and cascade genetic testing in the family of the victim. Sanger sequencing evolved in 1970's has previously been considered as the benchmark for its efficiency and reliability in examination of shorts strands of DNA. On the other side NGS has transfigured Post mortem Genetic analysis by allowing high productivity, high throughput DNA Sequencing of million fragments concurrently. In practice, NGS identifies possible variants, and Sanger sequencing acts as the final confirmation step before conclusions are drawn for legal or clinical purposes (14, 68).

3. Discussion:

The term "molecular autopsy" describes the use of genetic and molecular methods to identify the cause of death when toxicological and traditional autopsy results are unclear. In cases of sudden unexplained death, which are frequently connected to inherited cardiac channelopathies, cardiomyopathies, or metabolic diseases, it is very helpful. The integration of molecular autopsy with clinical genetics is expected to shape future practices in understanding unexplained death (33). Congenital coronary artery malformations and hypertrophic cardiomyopathy are examples of structural cardiovascular abnormalities that can be found after autopsy (74). Molecular autopsy uses multidisciplinary techniques that integrate genetics, pathology, forensic medicine, and bioinformatics. Unlooked- for unexplained deaths constantly leave families in a state of despair, searching for answers that conventional necropsies constantly fail to give. In numerous cases, there are no visible signs of complaint, leaving medical observers puzzled and loved bones in anguish. Over the times, molecular posthumous, powered by coming- generation sequencing (NGS), has surfaced as a vital tool in uncovering retired inheritable conditions. In forensic cardiogenetic, NGS has emerged as a crucial instrument that provides insightful information for postmortem examination (31). Posthumous inheritable analysis has helped families find check by relating causes in cases of child and immature adult deaths. Researchers used NGS to examine a large set of gene in young individual who died suddenly and were found to have structural problem in the heart (29). This technology is converting the study of unlooked- for child deaths, its eventuality to guide families and croakers toward preventative care was explained when heritable cardiac conditions are involved (17,16,10,12,2,5). Interpreting inheritable findings is a tricky procedure, indeed with the commitment. Since not all mutations readily indicate a problem, each variant needs to be estimated with perfection. Experts must strike a balance between clinical judgment and scientific understanding to help gratuitous solicitude or incorrect judgments. icing that findings from NGS are accurate is a critical step in molecular posthumous. Sanger sequencing help confirm results, reducing the chances of false cons that can beget gratuitous alarm. Emphasis of how substantiation is vital for giving families accurate information. Unconfirmed findings could lead to incongruous interventions or emotional torture. This process demands not only advanced technology but also thoughtful collaboration

among medical professionals, geneticists, and counselors, who must guide families through delicate opinions with care and empathy. Beyond relating the cause of death, molecular posthumous has practical counteraccusations for the living (59,44,45).

3.1 Collection and preservation: The accession of suitable natural samples is the original stage of molecular necropsy. Because the DNA is of similar high quality, it's preferable to use fresh or frozen towel, generally blood, spleen, or cardiac or cadaverous muscle. When fresh towel isn't available, formalin- fixed paraffin- bedded (FFPE) apkins can be used; still, the DNA in these samples may be broken up and changed chemically.

3.2 DNA extraction and evaluation of quality: After collection, the DNA is isolated by the usage of validated protocols for extraction which comprises of, ready - to - use purification kits or phenol - chloroform extraction method. Also, techniques like Gel electrophoresis, fluorescence spectrometry and spectral analysis are used to analyze the quantity, uncontaminated and genomic stability. High - yield DNA is vital for post - processing, particularly in massively parallel sequencing.

3.3 Genes screening for candidates: Sequencing of suspected genes are done using sanger sequencing particularly those related to SCD like - Potassium voltage - gated channel (KCNQ1), Potassium voltage - gated channel subfamily H member 2 (KCNH2), Sodium voltage - gated channel alpha submit 5 (SCN5A), and Ryanodine receptor 2 (RYR2) was a crucial element of conventional molecular autopsy. This methodology is confined by its reduced output and inability to cover disease - causing variants throughout the genome. In spite of being accurate and inexpensive for a pilot study.

3.4 NGS approaches: NGS enables high-throughput analysis of multiple genes simultaneously, making it especially useful for identifying variants associated with inherited arrhythmia syndromes and cardiomyopathies (8). It was highlighted that using multi-gene sequencing after death can significantly aid in diagnosing inherited arrhythmia syndromes (30). Evolution in decipherment of genetic code have fundamentally altered molecular autopsy. In forensic cardio genetics, next-generation sequencing has emerged as a crucial instrument that provides insightful information for postmortem examinations (31). Next generation sequencing let's simultaneous determination of many DNA sequences at once, complete genetic information in an economical and productive manner.

3.5 Targeted sequencing: The purpose of these panels is screen for genes most often found in cases of sudden unexplained death. They enable intent and speedy examination, broad reach, enhancing the diagnostic accuracy. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) are now widely applied in forensic cases, offering comprehensive coverage (1, 38).

3.6 Complete Genome Sequencing: It enables a broad perspective of both exons and introns, structural modifications and sequences that regulate gene expression. Though more data driven and expensive, it possesses the highest potential to reveal pathogenic implements.

3.7 Computational analysis of genome variation and classification of their significance: NGS creates a large quantity of source data needing developed step-by-step assembly line for conversion of raw sequencing data into organized genetic information: genetic variation analysis and network. Interpreting genetic data requires bioinformatics pipelines to filter, annotate, and classify variants according to international guidelines such as those from the American College of Medical Genetics (25, 58). Variants are sorted based on established rules like ACMG (American College of Medical Genetics and Genomics). Differentiating between pathogenic, likely pathogenic, innocuous, or VUS (Variants of uncertain significance) persists as an ongoing issue implies an association medical history, genetic and health research and operational testing. Despite the advances of NGS, Sanger sequencing remains vital for validation. It is often used to confirm variants of uncertain significance (VUS) and to validate pathogenic mutations detected by NGS, ensuring forensic reliability (72,20).

3.8 Family screening and validation: Identifying mutants by genetic analysis after post-mortem are frequently authenticated by Sanger sequencing, it attests to their genuineness significantly. This method has consequences not just the individual's life of the death, as members of the family can convey susceptible gene mutation (cascade testing in). Family members can facilitate in precautionary measures, preliminary screening as well as healthcare management. Collaborative databases and family segregation studies are essential to determine pathogenicity (68,46). Postmortem genetic testing raises ethical challenges, particularly around consent, communication of incidental findings, and responsibilities toward surviving relatives (54,21). Detecting an inheritable mutation allows croakers to screen cousins, offering early intervention and, in some cases, life- saving treatments. Extending outwardly, that rephrasing these inheritable findings into clinical care can significantly reduce the trouble of unborn incidents (24). After molecular autopsy results, crucial in assisting families in understanding inherited risks and potential long-term health effects (32)..Public enterprises are starting to integrate molecular posthumous into larger health systems. Comforting and transparent communication is just as important as the test results themselves because families still substantiation emotional challenges when defied with heritable problems. Looking toward the future, there's advisable that molecular posthumous will be more deeply integrated into medical practice. (26,27)

3.9 Legal consideration: Technologies in molecular autopsy also requires rigid conformity to code of ethics about approval, prudence, and summarizing. As genomic data is inherent to the family, proper guidance and effective communication with next kin are essential to the process. Moreover, the approach strengthens medico-legal investigations, providing scientifically defensible evidence (8). Courts increasingly demand molecular evidence in cases of unexplained death, reinforcing the need for accuracy, reproducibility, and transparency (50,35).

Table1: Molecular Autopsy Workflow: Integration of NGS and Sanger Sequencing

Step	Process	Role of NGS	Role of Sanger Sequencing	Outcome
1	**Case referral**	Guides the selection of genetic tests by considering broad panels or exome/genome sequencing.	Helps focus on known candidate genes when family history or clinical suspicion exists.	Initiation of molecular investigation in unexplained or sudden deaths.
2	**DNA extraction**	Provides high-quality DNA suitable for large-scale sequencing.	Ensures DNA integrity for targeted sequencing.	DNA obtained from postmortem tissues, blood, or preserved biological samples.
3	**Initial sequencing**	Performs broad genetic screening (targeted panels, exome, or genome) to detect multiple possible variants.	Can be applied for sequencing of specific candidate genes.	Wide identification of potential pathogenic variants.
4	**Bioinformatics analysis**	Uses computational pipelines for variant calling, annotation, and interpretation of novel/rare mutations.	Supports interpretation by confirming variants within candidate genes.	Prioritization of clinically and forensically significant mutations.
5	**Validation**	Provides large-scale data for cross-checking suspected variants.	Confirms identified variants with high accuracy; gold standard for single-gene verification.	Removal of false positives and assurance of result reliability.
6	**Reporting**	Supplies broad genetic context to link findings to cause of death and family risk test	Provides final confirmation for legal and clinical acceptance.	Establishes cause of death, assesses hereditary risk, gives forensic/legal reports.

4. Advantages of Molecular Autopsy

Molecular autopsy is progressively applicable to sudden deaths where invasive post – mortem examination lacks to provide response. The technology highly depends on genomic sequencing to deleterious mutations related to genetic diseases. Two genomic sequencing strategies conquer this field i.e. NGS and Sanger sequencing. Molecular autopsy provides critical insights where traditional autopsies fail, identifying genetic causes of sudden unexplained deaths (6,3). Every approach possesses distinct strength as well as limitations, and in application they are frequently employed in a complementary way. One of the greatest benefits of Sanger Sequencing is its incomparable accuracy with a percentage of error lesser than 0.001%. It is commonly known as standard authenticating variant. To ensure credibility in forensic and medical results, suspicious variants are usually re – tested by sanger before being reported, even when NGS is used for discovery. On the other hand, NGS offers an unparalleled scope. In a single experiment, it enables the simultaneous screening of hundreds to thousands of genes, or even complete exomes. Because sudden unexplained death frequently involves heterogenous gene pools, this is very helpful in molecular autopsy. The combined use of NGS and Sanger sequencing enhances both discovery and precision (28,18) also, stressed its significance in probing unlooked- for deaths among athletes, where external examination reveals nothing unusual. (10) What makes NGS especially important is its capability to screen hundreds of genes at formerly, offering explanations for conditions that preliminarily went undetected. It was highlighted that using multi-gene sequencing after death can significantly aid in diagnosing inherited arrhythmia syndromes (30). NGS provides a broad sweep, saving time and costs when sanger would need gene- by -gene testing (68). Additionally, NGS outperforms sanger in identifying uncommon or unexpected mutations. Sanger is restricted to candidate genes since it needs specific primers for known regions. However, NGS is more suited for research and new case studies since it may detect variations without presumptions (7). Variant interpretation is often the most challenging step, as many variants remain of uncertain significance, particularly in underrepresented populations (34,40). One of the greatest benefits lies in preventive medicine-genetic findings can inform screening and interventions for family members, potentially saving lives (55). Large datasets generated by NGS also contribute to population-specific reference databases, improving variant interpretation (1,38). Still, Sanger sequencing has an advantage in read length (up to about 900 bp), which makes it easier to estimate complicated or repetitious sections that short NGS reads would find delicate to read. Sanger continues to be briskly and more provident for small panels or single-gene evidence. NGS, on the other hand, dramatically lowers reversal times and costs per base for multi – gene panels or exome exploration, particularly in larger forensic or clinical examinations.

5. Limitations

The main drawbacks of sanger is its limited throughput. In cases of sudden death, where dozens of genes may be implicated, sequencing one fragment at a time is inefficient. Implementing molecular autopsy in forensic settings poses several practical and ethical challenges (60). With massively parallel sequencing, NGS gets around this, but it also brings with its additional

issues, like short read lengths and alignment error vulnerability. It is common for NGS to generate “variants of uncertain significance” (VUS). Forensic conclusions are complicated by these confusing findings, which can leave families in the dark (7). Variant interpretation remains difficult, with many classified as “variants of uncertain significance” (72,20). Since Sanger is typically utilized in a targeted manner, it rarely runs into this problem; but, because of its narrow scope, it may completely overlook pertinent alterations. Despite its promise, molecular autopsy has notable challenges. DNA quality can be compromised in postmortem samples, particularly in FFPE tissues (41,15). Technical differences between NGS platforms and lack of standardization across laboratories further complicate reproducibility (25,58). NGS is more prone to produce false positives and needs strong bioinformatics methods to filter errors, despite being sensitive to mosaicism and low – level alterations. sanger is the best choice for final confirmation because it provides clearer signals and higher specificity, although being less sensitive to mosaic mutations (70). For larger panels, NGS lowers the cost of sequencing each sample, but it requires costly infrastructure, processing poor, and skilled workers. In addition, costs remain a barrier in many forensic systems (34, 40). On the other hand, Sanger Sequencing is easier to use and more affordable, but it becomes slow and expensive when for large – scale research. Another limitation is the ethical complexity surrounding consent, disclosure of incidental findings, and family obligations (14,68). NGS frequently reveals accidental discoveries that are unrelated to the cause of death, which raises moral questions regarding consent, disclosure, and communicating family risks. Sanger rarely creates these kinds of problems since it is more focused (7).

6. Future Aspects

In recent years, molecular autopsies have become increasingly important, particularly when standard autopsies are unable to provide a satisfactory explanation for an abrupt and unexpected death. Also, research highlights how molecular autopsy discoveries can directly shape clinical practice and patient care (62). Under the microscope conditions such as cardiomyopathies, hereditary arrhythmia syndromes, and other genetic illnesses are frequently undetectable .Multi-gene testing has emerged as a valuable approach for uncovering genetic contributors to sudden death (67). The future of molecular autopsy lies in multi-omics integration—combining genomics with transcriptomics, proteomics, and metabolomics for a more holistic understanding (68,46). The use of genetic technologies like NGS and Sanger Sequencing have been facilitated by this gap and is anticipated to influence the future course of clinical and forensic investigations. As the cost of sequencing continues to drop, approaches such as whole exome sequencing (WES) and whole genome sequencing (WGS) may become routine parts of postmortem testing (9,21). These strategies not only improve the diagnostic yield but also allow for the discovery of novel mutations. In the near future, coupling NGS with advanced bioinformatics and machine learning tools will help resolve the current challenge of interpreting variants of uncertain significance (7). In the coming years, Next-Generation Sequencing is expected to take center stage in molecular autopsy work. Artificial intelligence and machine learning are being developed to improve variant interpretation (54,21). Unlike earlier methods, it can screen thousands of genes in parallel, making it possible to detect both common and rare mutations within a single study. Because the technology is

becoming faster and more affordable, approaches such as whole exome sequencing and whole genome sequencing are likely to become routine in postmortem analysis (9,21). International collaboration will be crucial for establishing reference databases, harmonizing methodologies, and ensuring equitable access to testing (42,11). Emphasis of significance of combining inheritable data with clinical histories to enhance preventative care, while stressed the need for collaboration between forensic experts and healthcare providers. (63, 36) But it's clear that technology can't break these problems by itself. Transparency, ethics, and compassion are essential for icing that families admit care at every stage. When executed courteously, molecular posthumous can offer not only scientific sapience but also mending and consolation during times of inconceivable loss (2, 5, 10, 12, 13, 16, 17, 24, 26, 27, 43, 44, 45, 52, 59, 63, 69, 71). Ethical frameworks are also evolving, with increasing attention to family-centered approaches and genetic counseling (50,35). Future directions also extend beyond solving individual cases. Large-scale molecular autopsy data could contribute to building population-specific variant databases, which in turn may guide preventive healthcare and family screening programs. However, ethical questions about privacy, data sharing, and consent will become more pressing as sequencing expands. Addressing these concerns will be as important as the scientific progress itself.

7. Conclusion

In clinical practice, molecular autopsy aids in detecting underlying hereditary cardiac disorders (65). The growing use of molecular necropsy has changed how we understand unforeseen or unexplained deaths. Traditional posthumous examinations remain important, yet numerous cases involving inherited diseases or subtle inheritable problems cannot be explained through pathology alone. In similar situations, genomic analysis has handed answers that were preliminarily out of reach, allowing investigators to uncover the retired part of DNA in mortality. However, challenges remain, as discuss the technical, interpretative, and ethical issues involved, such as sample handling, uncertain variants, and data privacy. Together, these studies emphasize the growing importance of molecular autopsy while calling for standardized protocols and careful application in forensic practice. (52) Molecular autopsy, through the integration of NGS and Sanger sequencing, has become an indispensable tool in forensic science and precision medicine. It bridges the gap between unexplained death and genetic diagnosis, serving both medical and legal needs (61,4). This shift not only helps to explain the cause of death but also offers families pivotal knowledge that may guide preventative healthcare. Coming- Generation Sequencing (NGS) has brought scale and speed to these examinations. It can dissect numerous genes at formerly and reveal rare or new variants that might else remain undetected. Its broad compass has made it the favored system for discovery, although challenges remain, similar as data interpretation, incidental findings, and the heavy reliance on bioinformatics. These difficulties show that high- outturn sequencing, while important, isn’t yet a stage-alone result. Sanger sequencing, despite being aged, continues to give the delicacy demanded for legal and clinical surrounds. While it cannot match the outturn of NGS, its part in attesting questionable or significant results is unmatched. While limitations remain in DNA quality, variant interpretation, and ethical considerations, ongoing advancements in sequencing technologies, bioinformatics, and global collaboration are

expected to enhance its accuracy and utility (64). Courts and forensic authorities frequently demand this position of perfection before inheritable findings are considered dependable. For this reason, the combination of NGS for disquisition and Sanger for evidence has come the most reliable approach in current forensic genetics. The reach of molecular necropsy goes far beyond the disquisition of death itself. relating inherited conditions can cover surviving cousins through early interventions, contribute to population databases, and strengthen public health systems. These benefits, still, bring ethical duties. Issues of sequestration, concurrence, and careful communication of results must remain central to insure responsible practice. unborn developments promise indeed lesser delicacy and effectiveness. Long- read sequencing, epigenetic analysis, and machine- literacy tools are formerly being explored and may overcome some of the current walls. Still, the combined use of NGS and Sanger sequencing will probably remain the foundation of secure molecular necropsy for times to come. Ultimately, molecular autopsy not only uncovers the hidden genetic causes of death but also transforms tragedy into an opportunity for prevention and intervention in surviving relatives (47,48,22,23). In the end, molecular necropsy is further than a specialized advance it is a step toward a deeper understanding of life, death, and heredity. Its capability to bridge drug, law, and family well-being ensures it'll remain a vital part of forensic wisdom.

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