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Research Paper
Altered Genes in Asbestosis Contamination

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ABSTRACT

Background: Today, many people have heard about the dangers of asbestos pollution. The use of asbestos has been banned in many countries. The only way to prevent asbestos pollution is to avoid breathing it in and coming into contact with it. The symptoms and damage caused by asbestos may not appear for years. Therefore, it is important to find changes in gene expression caused by asbestos pollution.

Methods: Initially, genes whose expression changes following asbestos exposure are extracted from relevant databases, such as GEO. From the gene expression data, genes that have changed significantly, as indicated by the adjusted p-value, are identified. Using undirected protein networks, these genes are entered into the internetwork structure. The formed network (interactome) is analyzed, and centrality indices are examined to determine central genes. Genes with higher centrality are selected. Gene-related biochemical pathways are extracted from the KEGG database. Related genes and biochemical pathways are validated through a literature review.

Results: Network analysis of genes altered by asbestos exposure identified key hub and bottleneck genes. From a set of 96 differentially expressed genes, three high-connectivity hubs (GAPDH, ACTB, IL6) and five critical bottlenecks (GAPDH, RPS27A, ACTB, VTN, APP) were prioritized. The consensus genes GAPDH and ACTB were found in both categories, underscoring their potentially pivotal role in the asbestos-response network.

Conclusion: This systems biology analysis identifies central molecular targets, particularly GAPDH and ACTB, within the asbestos-induced gene network. These findings provide a prioritized framework for future research into targeted genetic and therapeutic strategies aimed at mitigating asbestos-related pathologies.

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Introduction

Asbestos is the name of a group of mineral compounds of magnesium and silicon that are often found in nature as mineral fibers and rocks. These materials are used as refractory materials due to their high resistance to heat and fire. This mineral is used in the manufacture of a wide range of industrial goods such as false ceilings, tiles, some paper industries, and also, due to its high friction strength, in the manufacture of brake pads, clutches, and some other automotive parts [1].

For the first time in 300 BC, Theophrastus, who was a student of Aristotle, mentioned an unnamed substance in his book (On Stones) that burned when mixed with oil without causing any harm. Later, this substance was called asbestos. Some experts consider the dangers of this mineral to be far worse than cigarette smoke [2]. In some countries, the use of asbestos has been banned because it is very dangerous. Today, exposure mainly occurs through contact with damaged asbestos in old buildings or through historical occupational exposure in the construction, shipbuilding, and insulation industries, particularly between the 1970s and 1990s.

Exposure to asbestos increases the risk of lung diseases. Because this risk cannot be reduced by modifying handling methods, complete elimination of asbestos from industrial use remains the only effective preventive measure. Complications and diseases caused by asbestos fibers may persist for several years [3-7], often surfacing only years after exposure, a latency that makes understanding the underlying changes in gene expression especially important.

At the genomic level, asbestos fibers can directly induce mutagenesis and gene toxicity [4]. Among the genes that are altered in expression are BAP1, NF2, ALK, and CDKN2A [8-11].

Occupational lung cancer has a high mortality rate and is the most common cancer in France. Older studies have found conflicting results regarding the lobe of origin and histology of asbestos-related lung cancer (ARLC). Some studies have shown an upper lobe location similar to tobacco-related lung cancer, while others have found a lower lobe location. Although some studies identified adenocarcinoma as the most common cancer, a recent review of the literature by Nielsen and colleagues found no difference in location or cell type between ARLC and non-ARLC. They concluded that cell type and location of lung cancer are not useful in differentiating ARLC from other lung cancers. The prognosis of ARLC was no different from that of other lung cancers. The presence of pleural plaques indicated previous asbestos exposure, but was not a precancerous condition. Asbestosis was associated with high asbestos exposure and an increased risk of lung cancer [12].

For this reason, this study aims to identify genes with altered expression in response to asbestos exposure [4, 7, 13], to inform therapeutic strategies for this widely used but hazardous mineral [4, 13-16].

Materials and Methods

This study investigated differential gene expression in response to asbestos exposure through a bioinformatics approach. A systematic review of the literature was conducted utilizing the PubMed and Google Scholar databases to identify genes associated with asbestos exposure. Furthermore, gene expression datasets were retrieved from public repositories, including GEO.

From the compiled data, genes with significantly adjusted p-values were identified. These genes were mapped onto an undirected protein-protein interaction network using the STRING database. The resulting interactome was analyzed using Cytoscape software to calculate network centrality metrics. The differentially expressed genes were selected based on an adjusted p-value threshold of < 0.05. The hub genes were identified using a mean + 2 standard deviation cutoffs on degree value (threshold = 30.2). The top 5% of genes ranked by betweenness centrality were identified as bottleneck genes in the constructed PPI network.

The analysis focused on two key centrality indices: degree (measuring local connectivity) and betweenness (identifying potential network bottlenecks). Genes were ranked by these metrics to identify central players within the asbestos-responsive gene network.

Subsequently, the biological relevance of the top-ranking genes was assessed. Their involvement in biochemical pathways was investigated using the KEGG database, and their documented associations with asbestos toxicity were validated through an in-depth review of the scientific literature.

Results

Network analysis was performed on 96 genes identified as differentially expressed following asbestos exposure. These genes were used to construct a protein-protein interaction network (Figure 1).

Centrality analysis was first performed based on the degree metric. The average degree centrality for the 96-

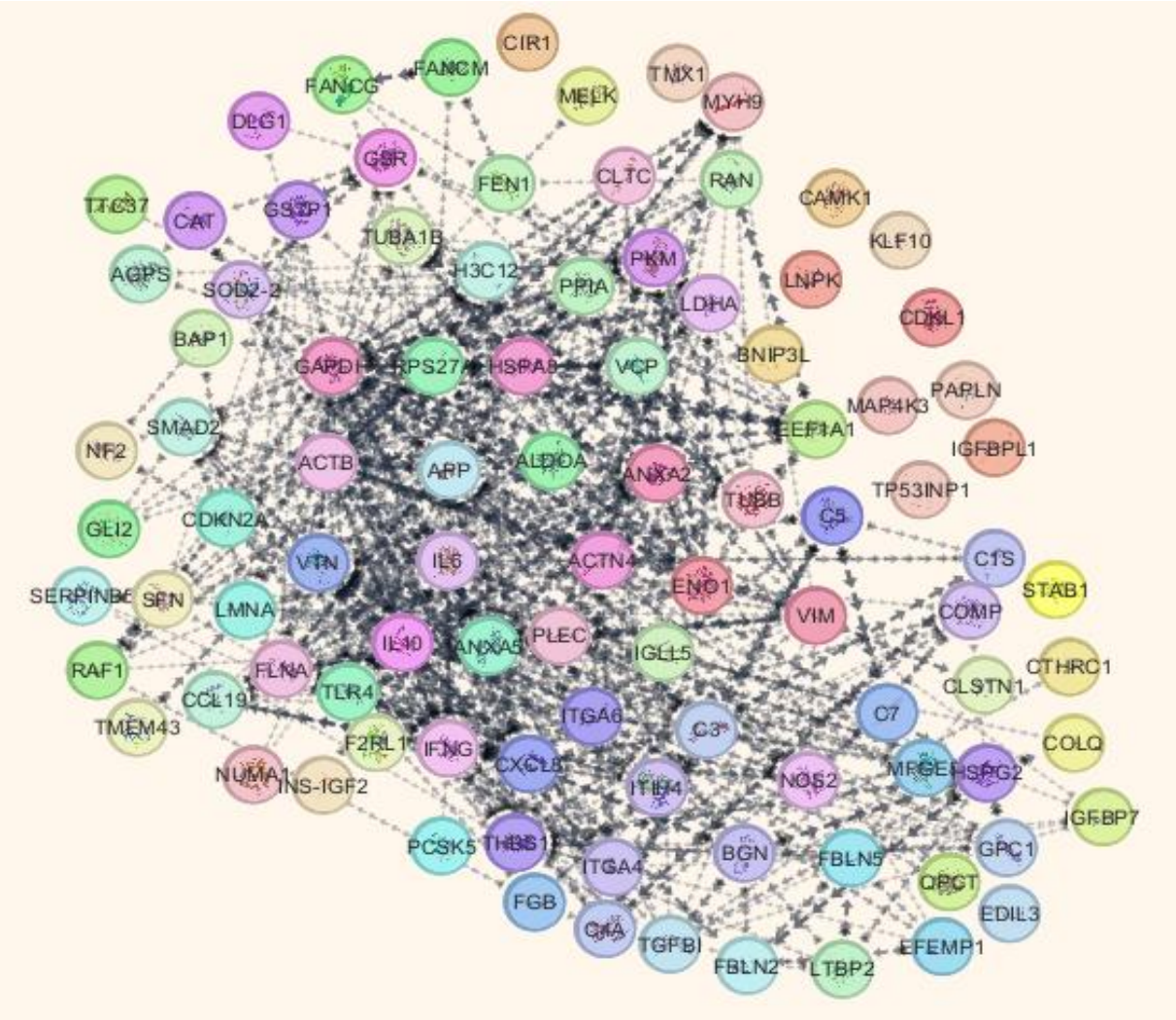


Figure 1. A view of the network and biological connections of 98 genes that are expressed differently in asbestos contamination.

gene network was 10.81 (standard deviation = 9.77). A cutoff was set at 30.2, calculated as the mean degree centrality plus two standard deviations (Mean + 2SD). Three genes, Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Beta-actin (ACTB), and interleukin (IL)-6, exceeded this threshold and were consequently identified as high-connectivity hubs within the network (Table 1).

Genes were subsequently ranked by descending betweenness centrality to identify potential network bottlenecks. The top 5% of genes (n=5), representing those with the highest betweenness scores, were GAPDH, RPS27A, ACTB, VTN, and APP (Table 2).

The complete list of 96 analyzed genes, along with their supporting references, is cataloged in Table 3.

Discussion

This study employed a network-based bioinformatics approach to identify and prioritize key genes dysregulated by asbestos exposure. By moving beyond simple lists of differentially expressed genes, centrality analysis provided a functional topology that highlighted genes occupying critical positions within the asbestos-responsive interactome. The consensus identification of GAPDH and ACTB as both high-degree hubs and high-betweenness bottlenecks underscores their potentially pivotal role in coordinating the cellular response to asbestos, bridging multiple pathogenic processes.

The centrality of GAPDH is particularly notable. GAPDH is often used as a “housekeeping” or loading control gene in gene expression analyses, which overlooks its complex role in growth and survival [17]. GAPDH has long been recognized as an important enzyme in energy metabolism, producing ATP and pyruvate via anaerobic glycolysis in the cytoplasm [18]. Actually, this is a redox-sensitive transcription factor classically associated with cell proliferation and tumor progression. Conditions such as oxidative stress impair the catalytic activity of GAPDH, leading to cellular senescence and apoptosis [19, 20].

Table 1. Degree of all genes. Genes are ranked by degree centrality (number of direct network interactions); GAPDH, ACTB, and IL6 show the highest connectivity, consistent with their identification as network hubs (see Results and Table 4).

Display name	Degree	Display name	Degree	Display name	Degree
GAPDH	46	TGFBI	13	IGFBP7	5
ACTB	43	SMAD2	17	CLTC	7
IL6	33	SOD2-2	14	BAP1	3
VTN	27	MYH9	12	MFGE8	7
APP	26	CXCL8	18	FANCM	3
RPS27A	23	SFN	11	AGPS	3
THBS1	29	ITGA4	13	LTBP2	6
IFNG	25	FBLN5	11	C1S	6
TLR4	25	TUBB	16	SERPIN B5	3
BGN	16	ITIH4	15	CLSTN1	2
IL10	23	PPIA	15	NUMA1	2
VCP	22	EEF1A1	14	GLI2	4
FEN1	9	IGLL5	6	BNIP3L	2
LMNA	17	RAF1	9	COLQ	2
H3C12	19	ITGA6	11	DLG1	2
HSPA8	24	GPC1	9	CTHRC1	1
CDKN2A	19	ACTN4	12	EDIL3	1
ANXA2	23	CCL19	8	F2RL1	1
ANXA5	25	NOS2	10	INS-IGF2	1
THBS1	29	FGB	8	MELK	1
IFNG	25	RAN	10	PCSK5	1
TLR4	25	C7	7	QPCT	1
HSPG2	16	GSTP1	9	TMEM43	1
VIM	21	TUBA1B	11	TTC37	1
PLEC	14	FANCG	4	CAMK1	0
ENO1	23	CAT	4	CDKL1	0
FLNA	21	EFEMP1	5	CIR1	0
C3	17	NF2	3	IGFBPL1	0
PKM	18	COMP	7	KLF10	0
C4A	13	ALDOA	12	LNPK	0
LDHA	15	C5	7	MAP4K3	0
GSR	13	FBLN2	6	PAPLN	0

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The expression of this gene is altered due to asbestos exposure. Thus, GAPDH may act as a central switch, where its altered expression or function dictates whether asbestos exposure leads to cell death, survival, or uncontrolled proliferation.

ACTB gene encodes one of six different actin proteins. Actin is a highly conserved protein that is involved in cell motility, structure, integrity, and intercellular signaling. ACTB has traditionally been regarded as an endogenous housekeeping gene and has been widely used as a reference gene/protein in quantifying expression levels in tumors [21]. Studies have shown that Mutations and altered expression of actin isoforms are associated with tumorigenesis [22]. In the context of asbestos, fibers physically interact with the cell surface and cytoskeleton, potentially making ACTB a direct sensor of this damage, translating mechanical insult into aberrant intracellular signaling that drives inflammation and transformation [23].

It is important to note that GAPDH and ACTB are canonical housekeeping genes routinely used as internal reference controls in gene expression studies [24]. Their prominent appearance in this dataset could, in principle, reflect a generalized cellular stress response rather than an asbestos-specific effect.

The other high-centrality genes delineate specific pathogenic axes. RPS27a, a ribosomal protein constituting the 40S small subunit of the ribosome, plays an important role in ribosome biogenesis [19]. Actually, it connects protein synthesis regulation (via ribosome biogenesis) and protein degradation (as a ubiquitin precursor). This links the pathways that regulate cell growth and manage stress, both of which are commonly taken over by cancer [18]. The change in expression of this gene in the presence of asbestos leads to its activation and the upregulation of many genes involved in cell proliferation and apoptosis [18]. Vitronectin (VTN), a multifunctional glycoprotein with various physiological functions, exists in plasma and the extracellular matrix. The protein encoded by this gene functions in part as an adhesive glycoprotein. Differential expression of this protein can promote either cell adhesion or migration as it links cells to the extracellular matrix through a variety of ligands. [25] Asbestos exposure alters the expression of this gene, disrupting and altering cell function [26].

The APP gene is involved in the processing of amyloid precursor proteins. This protein is found in many tissues and organs, including the brain and spinal cord (part of the central nervous system). Little is known about the function of the amyloid precursor protein. The amyloid precursor protein is cleaved by enzymes to produce smaller fragments (peptides), some of which are released outside the cell. Two of these fragments are called soluble amyloid precursor protein (sAPP) and beta-amyloid peptide (β). It interferes with the function of lung tissue cells indirectly by affecting the central nervous system and causes lung cancer [27].

IL-6 represents a central immune and inflammatory mediator [28, 29]. Its position as a high-degree hub supports its known role in the cytokine storm associated with severe inflammatory responses to asbestos, linking exposure to systemic inflammation and immune dysregulation. This cytokine affects most major

Table 2. Betweenness Centrality sources of all the Genes. Genes are ranked by betweenness centrality, reflecting their role as bridges between different regions of the network ; GAPDH, RPS27A, ACTB, VTN, and APP occupy the top five positions, identifying them as the principal network bottlenecks (see Results and Table 4).

Display name	Betweenness centrality	Display name	Betweenness centrality	Display name	Betweenness centrality
GAPDH	0.154500899	MYH9	0.008219335	BAP1	5.07E-04
RPS27A	0.088238449	CXCL8	0.007309013	MFGE8	5.00E-04
ACTB	0.078852109	SFN	0.007156386	FANCM	3.69E-04
VTN	0.075428169	ITGA4	0.007005809	AGPS	2.78E-04
APP	0.071699628	FBLN5	0.006602818	LTBP2	2.74E-04
IL6	0.066830222	TUBB	0.006371655	C1S	2.62E-04
THBS1	0.057731224	ITIH4	0.005423158	SERPINB5	2.46E-04
IFNG	0.047909085	PPIA	0.004875761	CLSTN1	1.79E-04
TLR4	0.044918912	EEF1A1	0.004475981	NUMA1	7.17E-05
BGN	0.040430833	IGLL5	0.004122428	GLI2	0
IL10	0.038542861	RAF1	0.003896779	BNIP3L	0
VCP	0.037023832	ITGA6	0.003274733	COLQ	0
FEN1	0.03066949	GPC1	0.002897317	DLG1	0
LMNA	0.030650125	ACTN4	0.002724465	CTHRC1	0
H3C12	0.030609763	CCL19	0.002326187	EDIL3	0
HSPA8	0.026793648	NOS2	0.00179181	F2RL1	0
CDKN2A	0.02491356	FGB	0.001735476	INS-IGF2	0
ANXA2	0.022170264	RAN	0.001493553	MELK	0
ANXA5	0.022157908	C7	0.001306848	PCSK5	0
HSPG2	0.021816757	GSTP1	0.001122102	QPCT	0
VIM	0.018689692	TUBA1B	0.001104407	TMEM43	0
PLEC	0.017637137	FANCG	0.001079792	TTC37	0
ENO1	0.017340816	CAT	0.001029611	CAMK1	0
FLNA	0.014473886	EFEMP1	9.58E-04	CDKL1	0
C3	0.014194956	NF2	8.94E-04	CIR1	0
PKM	0.014150958	COMP	7.38E-04	IGFBPL1	0
C4A	0.013546012	ALDOA	6.83E-04	KLF10	0
LDHA	0.011194207	C5	6.45E-04	LNPK	0
GSR	0.010780061	FBLN2	6.20E-04	MAP4K3	0
TGFBI	0.009269699	IGFBP7	5.98E-04	PAPLN	0
SMAD2	0.009080871	CLTC	5.10E-04	STAB1	0
SOD2-2	0.008857821	TMX1	0	TP53INP1	0

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biological systems and is used as a diagnostic marker.

The network model proposed here (Figure 1) integrates these findings and depicts how asbestos exposure may target these central genes. We hypothesize that the physical and oxidative stress of asbestos fibers concurrently disrupts cytoskeletal integrity (via ACTB), reprograms cellular metabolism (via GAPDH), and triggers a profound inflammatory signal (via IL6). Genes like RPS27A may modulate the global protein response to this multi-faceted stress, while VTN and APP could influence how cells interact with their altered microenvironment. The interconnectivity between these central players suggests a synergistic pathogenic network rather than isolated pathways.

A key limitation of this in silico study is its reliance on pre-existing datasets and predicted interactions. While centrality measures are powerful for prioritization, the precise mechanistic roles of these genes in asbestos-related diseases require validation through in vitro and in vivo experimental models. Furthermore, future work integrating multi-omics data (e.g., epigenetics, proteomics) could reveal the upstream regulators and downstream effectors of this core network.

Beyond their mechanistic relevance, these findings carry direct implications for forensic and occupational medicine. In cases of suspected occupational asbestos exposure, particularly where a definitive exposure history is unavailable or disputed, molecular biomarkers derived from this network could complement established diagnostic criteria by providing objective, quantifiable evidence of asbestos-related cellular injury. Incorporating such biomarkers into forensic toxicology panels may aid retrospective

Table 3. References of all genes. This table lists the literature source supporting the inclusion of each of the 96 differentially expressed genes in the asbestos-response network.

Display name	References	Display name	References
GAPDH	[30]	FGB	[31]
RPS27A	[32]	RAN	[33]
ACTB	[34]	C7	[35]
VTN	[36]	GSTP1	[4]
APP	[4]	TUBA1B	[4]
IL6	[37]	FANCG	[38]
THBS1	[39]	CAT	[40]
IFNG	[41]	EFEMP1	[4]
TLR4	[4]	NF2	[42]
BGN	[4]	COMP	[43)
IL10	[44]	ALDOA	[45]
VCP	[46]	C5	[47]
FEN1	[48]	FBLN2	[45]
LMNA	[49]	IGFBP7	[45]
H3C12	[4]	CLTC	[50]
HSPA8	[51]	BAP1	[4]
CDKN2A	[52]	MFGE8	[50]
ANXA2	[53]	FANCM	[54]
ANXA5	[55]	AGPS	[4]
HSPG2	[4]	LTBP2	[4]
VIM	[4]	C1S	[56]
PLEC	[50]	SERPINB5	[56]
ENO1	[57]	CLSTN1	[56]
FLNA	[50]	NUMA1	[56]
C3	[58]	GLI2	[4]
PKM	[59]	BNIP3L	[4]
C4A	[45]	COLQ	[60]
LDHA	[61]	DLG1	[56]
GSR	[62]	CTHRC1	[56]
TGFBI	[63]	EDIL3	[56]
SMAD2	[50]	F2RL1	[50]
SOD2-2	[45]	INS-IGF2	[50]
MYH9	[50]	MELK	[64]
CXCL8	[45]	PCSK5	[50]
SFN	[50]	QPCT	[50]
ITGA4	[4]	TMEM43	[45]
FBLN5	[4]	TTC37	[65]
TUBB	[66]	CAMK1	[67]
ITIH4	[68]	CDKL1	[65]
PPIA	[69]	CIR1	[65]
EEF1A1	[50]	IGFBPL1	[4]
IGLL5	[4]	KLF10	[42]
RAF1	[70]	LNPK	[4]
ITGA6	[50]	MAP4K3	[56]
GPC1	[56]	PAPLN	[71]
ACTN4	[56]	STAB1	[4]
CCL19	[45]	TMX1	[72]
NOS2	[50]	TP53INP1	[65]

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Table 4. General information on the 6 consensus hub and bottleneck genes with high centrality in the asbestos-response network. These genes were prioritized based on their high degree and/or betweenness centrality (Tables 1–2) and represent the candidate biomarkers discussed in the Results and Discussion.

Gene	Full name	Description	Source
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase	An important enzyme for energy metabolism and the production of ATP and pyruvate via anaerobic glycolysis in the cytoplasm	[16-20]
RPS27A	ribosomal protein S27a	A gene that produces a regulatory protein in the human body.	[16-21]
ACTB	Aactin beta	The ACTB gene provides instructions for making a protein called beta (β)-actin, which is part of the actin protein family.	[22, 23]
VTN	Vitronectin	Differential expression of this protein can promote either cell adhesion or migration as it links cells to the extracellular matrix through a variety of ligands	[25, 26]
APP	amyloid beta precursor protein	This gene encodes a cell surface receptor and transmembrane precursor protein	[27]
IL6	Interleukin-6	is a Protein Coding gene. Elevated IL-6 concentrations are associated with several inflammatory diseases and malignancies	[28]

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exposure assessment, strengthen causal attribution in occupational disease litigation, and support post-mortem investigations in which tissue-based molecular profiling can corroborate a documented history of asbestos exposure.

Conclusion

In conclusion, this network analysis reframes the molecular response to asbestos from a catalog of altered genes to an interconnected system with clear topological leaders. The consensus centrality of GAPDH and ACTB marks them not merely as biomarkers but as potential master regulators and high-value therapeutic targets. Disrupting their function or

the critical links they maintain in the network may offer a novel strategy for intervening in the pathogenesis of asbestosis and asbestos-related cancers, moving us closer to a mechanistic, gene-targeted therapeutic approach. From a practical standpoint, we recommend that occupational health surveillance programs evaluate GAPDH and ACTB expression profiling as adjunct biomarkers for the early detection of asbestos-related cellular injury in at-risk workers, and that forensic pathology and occupational medicine practitioners consider their diagnostic value alongside established radiological and histopathological criteria in cases of disputed asbestos exposure. Prospective validation in exposed cohorts, together with standardized expression-based cutoff values, will be needed before these targets can be adopted in routine clinical or medico-legal practice.

Ethical Approval

None.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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