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JSM Biomarkers

Review Article

How can we Track Psychosis? A Scoping Review of Biomarkers of Transition in Subjects at Risk

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Submitted: 26 April 2022

Accepted: 24 May 2022

Published: 27 May 2022

ISSN: 2578-3815

Keywords
• Psychosis; Biomarkers; Schizophrenia; High risk; Transition

Abstract

In recent years, research has made progress in attempting to foresee the development of psychosis. Several definitions of clinical syndromes and/or familial susceptibility have been proposed to predict transition to psychosis. Among subjects identified as being at risk, it is expected that almost a third of them will eventually transition to psychosis. Although these definitions clearly represent sensitive tools, they lack specificity and rely on clinical judgment. Hence, biomarkers are being investigated as objective biological assessment tools to refine the prediction of psychosis. This scoping review focuses on the biomarkers currently under investigation. We reviewed the studies published since January 2015 that put forth a biomarker associated with the risk of developing schizophrenia (SZ) or a SZ spectrum disorder. A search of the MEDLINE (via PubMed), EMBASE, PsycINFO (via OVID) and Cochrane Central Register of Controlled Trials electronic databases was conducted and 96 studies that investigated predictive biomarkers in the at-risk population were included. More precisely, we reviewed these studies focusing on study design, the effect size of the association between biomarkers and psychosis, and evidence for replication. The review revealed several biomarkers, including reduced duration mismatch negativity, reduced 40 Hz auditory steady-state responses and impaired gyrification parameters. In this paper, we discuss the lack of clinical use of these potential tools and the criteria that biomarkers must meet to be considered as medical guidelines in psychiatry.

ABBREVIATIONS

SZ: Schizophrenia; SMI: Severe Mental Illness; HR: High-risk subjects; FHR: Familial "genetic" high-risk; CHR: Clinical High Risk; ARMS: At-risk mental state; UHR: Ultra-high risk; PRS: Psychotic Risk Syndrome; REP: Subjects at *Risk of first-Episode Psychosis*; REP-T: REP subjects *who later Transitioned to psychosis*; REP-NT: REP subjects *who did Not Transition*; sMRI: Structural Magnetic Resonance Imaging; LGI: Local Gyrification Index; GMV: Gray Matter Volume; ACG: Anterior Cingulate Gyrus; EEG: Electroencephalogram; dMMN: Duration Mismatch Negativity; fMRI: Functional Magnetic Resonance Imaging; rs-fMRI: Resting state functional Magnetic Resonance Imaging; ASSR: Auditory steady- state responses; MEG: Magnetoencephalography; MRS: Magnetic Resonance Spectroscopy; fNIRS: Functional near-infrared Spectroscopy; PET: Position Emission Tomography; EMG: Electromyography; NS: Niacin Skin Sensitivity; REP^{+}: REP subjects with a higher level of deficits; REP^{-}: REP subjects with a lower level of deficits; FEP: Subjects with first-episode psychosis; PFC: Prefrontal Cortex; IPL: Inferior Parietal Lobule; PCC: Posterior Cingulate Cortex; FCS: Functional Connectivity Strength; ReHo: Regional Homogeneity; ITG: Inferior Temporal Gyrus; DTI: Diffusion Tensor Imaging; DWI: Diffusion-weighted Imaging; TSPO: Translocator Protein; ERG: Electroretinography; HRV: Heart Rate Variability

INTRODUCTION

Schizophrenia (**SZ**) spectrum disorders are mostly chronic mental disorders, characterized by psychotic, positive or negative symptoms and cognitive deficits [1,2]. The full extent of these diseases usually strikes in early adulthood or adolescence [3]. However, a scientific consensus says that neurobiological alterations emerge even before the first episode of psychosis [4-6], suggesting a neurodevelopmental component [7-9] likely to be measured as a predictive biomarker in the population at risk. Hence, finding indicators of the biological processes underlying the neurodevelopmental trajectories of SZ could offer the opportunity to track early signs of mental illness in order to prevent or delay transition to psychosis.

Having a biological parent with a severe mental illness (**SMI**) – such as SZ– is known to be a psychosis risk factor among offspring referred to as high-risk subjects (**HR;** or familial "genetic" high-risk; **FHR**) [10]. In addition to this genetic susceptibility, clinical symptoms like subthreshold or attenuated psychotic symptoms and impairment in day-to-day functioning have also been identified as psychosis risk factors [11]. In recent literature, subjects at clinical risk for psychosis are referred to as subjects with a clinical high risk (**CHR**), an at-risk mental state (**ARMS**), an ultra-high risk (**UHR**), a psychotic risk syndrome (**PRS**), or an attenuated psychosis syndrome (see Table 1 for definitions and

Table 1: Definitions of subjects at Risk of first-Episode Psychosis (REP) found in current literature are provided below.

	REP Definition	Criteria
Genetic risk	High-risk (**HR**) or familial high-risk (**FHR**)	First-degree familial history of SZ spectrum disorder [67]
Clinical risk	Clinical high risk (**CHR**)	1- Diagnostic criteria for prodromal syndrome 2- No current DSM Axis I disorder 3- No history of or current treatment with antipsychotic medication [76]
	At-risk mental state (**ARMS**)	1- No previous episode of overt psychosis + One or more: 2- Attenuated psychotic symptoms 3- Brief and limited intermittent psychotic symptoms 4- Genetic risk 5- Deterioration syndrome [44]
	Ultra-high risk (**UHR**)	One or more: 1- Attenuated positive symptoms 2- Brief limited intermittent psychotic symptoms 3- Mental state and trait risk factors with functional decline [116]
	Psychotic risk syndrome (**PRS**)	One or more: 1- Attenuated psychotic symptoms 2- Brief limited intermittent psychotic symptoms 3- Familial history of psychosis in first-degree relatives 4- Change in functioning occurred within the last year and maintained at least one month [11]

references). For the purpose of this review, subjects falling into any of these genetic and/or clinical susceptibility categories will be referred to overall as subjects at *Risk of first- Episode Psychosis* (**REP**). As much as 30% of REP subjects will eventually develop an SMI in adulthood, especially after experiencing a first episode of psychosis [12,13]. It remains that most of them will not develop a SZ spectrum disorder. Hence, based solely on this classification (REP), it is impossible to make any prediction on the onset of individual psychosis [14]. Furthermore, early intervention trials among REP subjects to delay or prevent the onset of psychosis (e.g., cognitive behavioral therapy, omega-3 fatty acids or integrated psychotherapy) have shown moderate efficiency [15]. This finding could be partly due to the difficulty of specifically treating subjects slipping into psychosis. Thus, clinical trials would benefit from an enhanced capacity to identify, among REP subjects, those who are more likely to develop psychosis. Given the lack of specificity in the REP classification, biomarkers are needed to better identify the minority of individuals who will slip into psychosis.

Biomarkers are objective indicators of biological processes [16] that are already implemented in preventive medicine. Although research on biomarkers in the field of psychiatry has made significant progress since the beginning of the new millennium 2000s [16-18], there is yet to be a translational use in the clinical setting. Why? What is the current state of research on psychosis biomarkers? By reviewing studies published since 2015, we have mapped the available evidence in order to scope predictive biomarkers in REP subjects. We highlighted the study design used, the effect size of the correlation between biomarkers and psychosis, and the evidence for replication. In this paper, we will discuss the lack of clinical psychiatry tools and we will attempt to identify potential biomarkers for future clinical use.

METHOD

We have decided to do a scoping review [19] to cover the body of recent literature on biomarkers associated with the risk of developing a SZ-related disorder. We searched for papers on studies that investigated predictive biomarkers measured in REP subjects. We used the MEDLINE (via PubMed), EMBASE, PsycINFO (via OVID) and Cochrane Central Register of Controlled Trials electronic databases to search for a combination of indexing terms and free-text words in titles or abstracts referring to our population of interest: “Clinical high risk state for psychosis” OR “High risk state for psychosis” OR “Ultra High risk for psychosis” OR “Clinical high risk for psychosis” OR “Clinical risk for psychosis” OR “at risk mental state for psychosis” OR “risk for psychosis” OR “psychosis risk” OR “psychosis high risk” OR “psychosis prediction” OR “psychosis prodrome” OR “prodromal psychosis” OR “psychosis*” OR “psychotic” OR “psychotic disorder” OR “psychotic episode” OR “early psychosis” OR “first episode” OR “schizophrenia” OR “schizoaffective” OR “Schizophrenia Spectrum and Other Psychotic Disorders”, combined with the terms “biomarker” OR “marker”. This review included English-language papers only published since January 2015, excluding conference abstracts, editorials, book chapters, animal studies, reviews and meta-analysis.

As shown in the flowchart (Figure 1), the search yielded 2,945 potential studies after duplicates were removed. Of those, 200 studies met inclusion criteria (predictive biomarkers measured in REP subjects) after abstracts were screened and 96 studies remained after the full texts were reviewed.

RESULTS

Ninety-six articles met our inclusion criteria (Figure 1). The results from the 19 studies addressing transition to psychosis (Section 1) will be presented first, followed by the results from the studies on the state of being a REP subject, without observing transition (Section 2). Each section will be then subdivided according to the type of biomarker (brain, blood, genetic, eye or others), study design and group comparison.

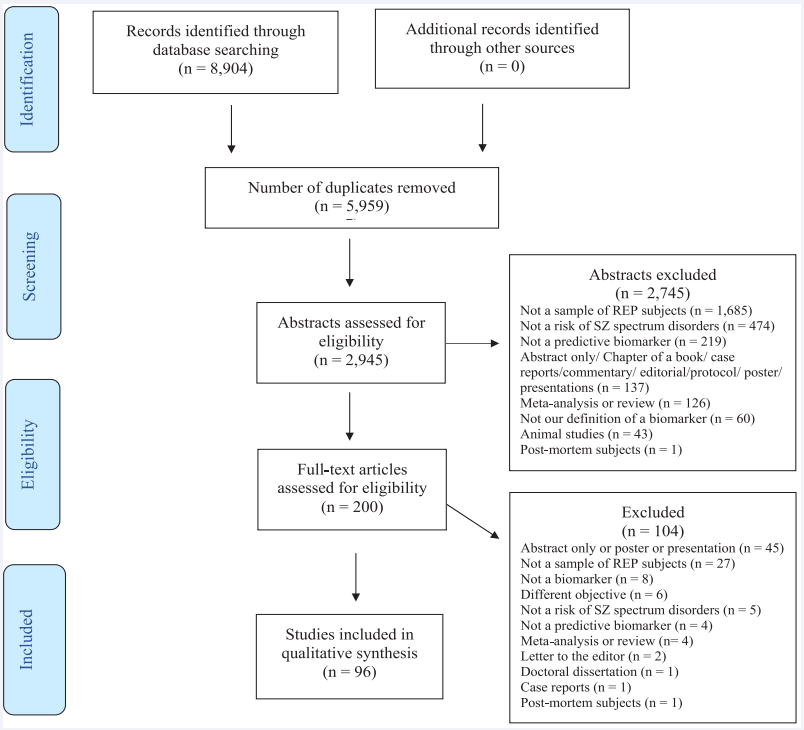

Figure 1 Flowchart of Selection Process.

Psychosis transition biomarkers

Given that not all REP subjects will eventually transition to psychosis, our main interest was to review the tools (biomarkers) likely to predict the subjects who will transition. Follow-up studies allow for the assessment of such transition. Table 2 reports on the 19 follow-up studies conducted since 2015 (summarized below) to compare a group of REP subjects *who later Transitioned to psychosis* (**REP-T**) with either a group of REP subjects *who did Not Transition* (**REP-NT)** or a group of not-at-risk control subjects**.**

Investigation of brain biomarkers as predictors of transition to psychosis: In five studies, REP-T and REP-NT subjects were compared through structural magnetic resonance imaging (sMRI). The REP-T subjects had: 1- higher brain transitivity (p = 0.042; the same increase was observed in REP-T subjects compared to control subjects; $p < 0.001$) [14]; 2- higher local gyrification index (LGI) in the left occipital region (p = 0.014) [20]; and 3- decreased gray matter volume (GMV) in prefrontal, perisylvian and subcortical structures ($p < 0.001$) [21]. Also, in a cohort of 476 REP subjects, a multivariate model involving the brain age gap biomarker was found to be predictive of transition to psychosis ($p < 0.05$) [22]. Furthermore, although no differences in the anterior cingulate gyrus (ACG) morphology were found between REP-T and REP-NT subjects, compared with control subjects, REP-T subjects showed increased surface areas and decreased thickness of the left ACG (p = 0.025) [23].

In five other studies, REP-T and REP-NT subjects were compared using electroencephalogram (**EEG**) assessments. The REP-T subjects had: 1- prolonged P300 latencies (p = 0.011 and 0.022) [24], 2- decreased EEG microstate D coverage and occurrence (p = 0.003 and < 0.001, respectively) [25], and 3- reduced amplitude of duration mismatch negativity (**dMMN**) at baseline (p = 0.017; the same decreased dMMN was observed in REP-T subjects compared to control subjects; p = 0.004) [26]. Additionally, REP-T subjects had a reduced dMMN amplitude at follow-up, compared with the baseline. Furthermore, in a cohort of 298 REP subjects, REP-T subjects were found to have a reduced auditory target P3b amplitude; a smaller auditory target P3b amplitude was also associated with a shorter lead time to the onset of psychosis (p = 0.048) [27]. In a new cohort of 33 REP subjects, Hamilton et al. [28] added the visual modality of target P3b. As a result, they found that both the auditory and visual target P3b amplitudes were reduced in REP-T subjects and predicted lead time to the onset of psychosis (p = 0.002). Along the same lines, greater deficits in target P3b predicted more imminent risks of psychosis onset. Assessment through resting state functional magnetic resonance imaging (**rs-fMRI**) showed that REP-T subjects had lower medial prefrontal cortex connectivity ($p < 0.001$ and p = 0.046, respectively) compared with REP-NT subjects and control subjects [29]. At follow-up, it was found that REP subjects with lower connectivity were more likely to transition to psychosis.

Additionally, compared with REP-NT subjects and control subjects, REP-T subjects had impaired and reduced amplitude in the right thalamus during 40 Hz auditory steady- state responses (**ASSR**) measured with magnetoencephalography (**MEG**; p = 0.049 and 0.011, respectively) [30]. Moreover, transition to psychosis was predicted by 40 Hz ASSR impairments: ASSR activity in the right thalamus correctly classified 76.9% of the REP-T subjects.

Through functional near-infrared spectroscopy (**fNIRS**)

Table 2: Biomarkers significantly related to transition to psychosis resulting from follow-up studies of subjects at risk of psychosis (REP subjects) are presented below with their corresponding effect sizes. Subjects who transitioned to psychosis are labeled REP-T, while those who did not transition to psychosis are labeled REP-NT.

				REP Subjects			FoU (Y)	Psychosis Transition		CT (n)	Group Comparison			
											REP-T vs. REP-NT		REP-T vs. CT	
		Reference	Biomarker	Def	N	Mean age or Range		Yes (n)	No (n)		Trend	ES or p-value	Trend	ES or p-value
Brain	sMRI	Das et al. (2018) [14]	Brain transitivity	ARMS	79	24.4	3.8	16	63	44	↑	Hg= 1.76	↑	Hg= 1.41
		Sasabayashi et al. (2017) [20]	LGIa	ARMS	90	21.4	4.9	21	69	n/a	↑	*p*=0.01	n/a	n/a
		Koutsouleris et al. (2015) [21]	Gray matter volumeb	ARMS	73	24.8	4.4	33	40	n/a	↓	PPV=80.6 NPV=81.0	n/a	n/a
		Chung et al. (2019) [22]	Brain age gap	CHR	476	12_35	2	67	409	n/a	MuM	HazR= 1.21	n/a	n/a
		Takayanagi et al. (2017) [23]	Surface areas of the left ACG	ARMS	73	21.7	2	17	56	74	n/a	n/a	↑	*d*=0.69
			Thickness of the left ACG								n/a	n/a	↓	*d*=−0.53
	rs-fMRI	Ilzarbe et al. (2021) [29]	Medical prefrontal cortex connectivity	CHR	39	15.5	1.2	15	24	27	↓	*p* < 0.001 ROC=0.83 Sens=0.79 Sp=0.79	↓	*p* = 0.046
	EEG	Hamilton, Roach et al. (2019a) [27]	Auditory target P3b amplitude	PRS	298	19.2	2	73	225	n/a	↓	*d*=0.26 HazR = 1.45	n/a	n/a
		Hamilton, Woods et al. (2019b) [28]	Auditory and visual target P3b amplitudes	PRS	33	16.2	1.8	15	18	n/a	↓	*d* = 0.62 HazR = 1.89	n/a	n/a
		Bock et al.-2020 [25]	Microstate D coverage	UHR	54	25.5	3	20	34	25	↓	*d*= -0.84	n/a	n/a
			Microstate D occurrence								↓	*d*= -1.24	n/a	n/a
		Higuchi et al. -2021 [24]	P300 latency	ARMS	33	19.2	3.5	8	25	28	↑	*p*= 0.039	n/a	n/a
			P300 amplitude								ø	ø	↑	*p*=0.011
		Tateno et al. (2021) [26]	dMMN amplitude	ARMS	39	18.5	2	11	28	22	↓	*p*= 0.017	↓	*p*=0.004
	MEG	Grent-'t-Jong et al. (2021) [75]	40 Hz ASSR in right thalamus	CHR	116	22	1.5	13	97	49	↓	*d*=0.72	↓	*d*=1.02
											LRM	ROC=0.70	n/a	n/a
			40 Hz ASSR in right hippocampus								ø	ø	↓	*d*=0.88
	fNIRS	Koike et al. (2017) [31]	Centroid value of brain waveforms	UHR	34	21	1	6	28	33	n/a	n/a	MuM	Sens= 6/6
	EMG	Cadenhead et al. (2020) [32]	Acoustic startle latency	CHR	543	18.7	1	58	255	218	↑	ROC=0.65 in females ROC=0.54 in males	n/a	n/a
Blood	Fatty Acids	Clark et al. (2016) [33]	Nervonic acid levels Omega 3d	UHR	40	12.9 - 22.3	1	11	29	n/a	MuM	Sens = 81.80% Sp = 78.6%	n/a	n/a
	Inflammatory biomarker	Föcking et al. (2016) [34]	Interleukin 12/23	ARMS	39	16.1	1	11	28	n/a	↑	Fold change: 1.57	n/a	n/a
Genetic		Jeffries et al. (2016) [35]	Leukocytes miRNA expression	CHR	67	18.4	2	30	37	27	↓	ROC= 0.86	↓	ROC= 0.75
Others	ORS	Langbein et al. (2018) [36]	NS	UHR	79	20.6	1	13	66	180	n/a	n/a	↓	Partial η2= 0.041
	Salivary samples	Worthington et al. (2021) [37]	Salivary cortisol	CHR	417	18.7	2	54	363	n/a	↑	HazR = 21.5	n/a	n/a

using the timing of frontal activity (Centroid value), all the REP-T subjects (100%; 6/6) were successfully classified into the psychosis spectrum group, whereas 83.3% of them were correctly classified based on the intensity of frontal activity (Integrated value) [31].

Finally, compared with electromyography (**EMG**) assessments of REP-NT subjects, REP-T subjects had longer acoustic startle latencies. This difference in transition groups was more prominent in females ($p < 0.05$) [32].

Investigation of blood biomarkers as predictors of transition to psychosis: Both omega-3 and nervonic acid levels predicted transition to psychosis ($p = 0.023$ and 0.041, respectively) [33]. Also, REP-T subjects had increased Interleukin 12/23 compared with REP-NT subjects ($p = 0.003$) [34].

Investigation of genetic biomarkers as predictors of transition to psychosis: Compared with REP-NT subjects and control subjects, REP-T subjects had much weaker miRNA group orchestration ($p = 0.012$) [35].

Investigation of other types of biomarkers as predictors of transition to psychosis: Although no niacin skin sensitivity (NS) differences were observed between REP-T and REP-NT subjects, REP-T subjects were found to have decreased NS compared with control subjects ($p = 0.005$, 0.024 and 0.041) [36]. Also, higher levels of salivary cortisol were predictive of transition to psychosis in a cohort of 417 REP subjects, among which 13.2% transitioned to psychosis ($p = 0.004$) [37].

Biomarkers among REP subjects, before transition to psychosis

As an alternative to relating a biomarker to transition to psychosis, other studies compared REP subjects with not-at-risk-control subjects or stratified the group of REP subjects under study into subgroups of subjects with a higher (**REP$^+$**) and lower level of deficits (**REP$^-$**). Table 3 presents a summary of results from 85 studies published since 2015.

Brain biomarkers:

Structural magnetic resonance imaging (sMRI) assessments: Kambeitz-Ilankovic et al. [38] stratified REP subjects according to their long-term functioning levels: REPs$^+$ (low-functioning level REP subjects, i.e. GAF score < 70) versus REPs$^-$ (high-functioning level REP subjects, i.e. GAF score ≥ 70). The REP$^+$ group had: 1- increased surface areas of the left precentral ($p < 0.001$), lateral occipital cortices ($p = 0.032$), right superior temporal ($p < 0.001$) and lateral occipital cortices on the right hemisphere ($p < 0.001$); 2- reduced cortical areas on the left hemisphere (p between 0.000 and 0.035); and 3- reduced surface values on the right hemisphere (p between 0.000 and 0.032). Furthermore, at follow-up, the neuroanatomical predictor distinguished REP$^+$ from REP$^-$ (PPV = 78.6; NPV = 84.6).

Compared with control subjects, REP subjects showed: 1- increased local gyrification index (**LGI**) in bilateral frontal ($p = 0.0001$), temporal ($p = 0.0448$), parietal ($p = 0.0001$) and occipital ($p = 0.0001$) regions [20] (LGI was also higher in REP-T subjects compared with REP-NT subjects; Table 2); 2- decreased cortical gyrification, including (a) the LGI in the lateral orbitofrontal, superior bank of the superior temporal sulcus, anterior isthmus of the cingulate and temporal poles ($p < 0.05$); (b) the mean curvature index in the cingulate, post-central and lingual gyrus ($p < 0.05$); and (c) the sulcal depth in parietal, superior temporal sulcus and cingulate regions ($p < 0.05$) [39]; 3- lower cortical gyrification (hypogyria) in clusters, including medial parieto-occipital and cingulate regions ($p < 0.001$) [40]; 4- larger white matter volumes in the left Crus I/II, but only in males ($p = 0.031$; $g = 0.856$; male REP subjects had also higher white matter volumes in the right Crus I/II compared with subjects with first-episode psychosis (**FEP**; $p = 0.007$; $g = 1.248$) [41]; 5- larger putamen ($p < 0.001$) [42]; 6- decreased volume of the amygdala lateral nucleus ($p = 0.0006$) [43]; 7- decreased pineal gland volume ($p = 0.015$; $d = -0.38$ to -0.54) [44]; and 8- decreased cortical thickness in the left prefrontal cortex (**PFC;** $p < 0.001$), the right PFC ($p < 0.001$), the left inferior parietal lobule (**IPL;** $p = 0.018$) and the right IPL ($p = 0.043$) [45].

Functional magnetic resonance imaging (fMRI) assessments: Compared with control subjects, REP subjects had: 1- differences over time in connectivity between Crus I and the occipital cortex ($p = 0.008$) [46]; 2- increased hippocampus/amygdala activity during neutral faces processing ($d = 0.987$) [47]; 3- reduced dorsolateral prefrontal activity during failed inhibition ($p < 0.05$; $d = 0.980$) [47]; 4- greater probabilistic category learning task activity (i.e. the Weather Prediction Task) in several parietal, occipital and one temporal regions ($p < 0.01$) [48]; 5- decreased striatal activation ($p < 0.01$; $d = 0.86$), activation in the associative striatum ($p < 0.01$; $d = 0.89$) and activity in multiple cortical regions connected to the associative striatum ($p < 0.01$; $d = 0.70$ to 0.89) [48]; 6- lower brain activation in face processing areas ($p = 0.003$) [49]; 7- lower activity of a network involving the bilateral auditory cortices, the thalamus and frontal brain regions, mediated by gamma oscillation ($p < .01$) [50]; and 8- lower brain activation in the left ($p = 0.04$; $d = 0.58$) and right caudate ($p = 0.04$; $d = 0.57$) [51], decreased activation in the associative cortico-striatal network being negatively associated with variability in the grip force in REP subjects.

Resting state functional magnetic resonance imaging (rs-fMRI) assessments: Decross et al. [52] stratified REP subjects according to their level of delusional beliefs: 43 REPs$^+$ (high level) versus 44 REPs$^-$ (low level). REPs$^+$ had greater connectivity between the amygdala and visual cortex ($p < 0.001$). Likewise, Wang et al. [53] stratified REP subjects according to their level of subthreshold psychotic experiences: 22 REPs$^+$ (moderately elevated level) versus 22 REPs$^-$ (consistently low level). REPs$^+$ had lower rates of moment-to-moment engagement of brain networks involving the visual and salience networks ($p < 0.001$; the same result was observed compared with control subjects).

Compared with control subjects, REP subjects showed: 1- increased medial prefrontal cortex (**mPFC**) – posterior cingulate cortex (**PCC**) connectivity in resting-state analyses ($p = 0.0037$), but decreased mPFC–PCC connectivity in task connectivity analyses ($p = 0.03$) [54]; 2- increased functional connectivity strength (**FCS**) in the left calcarine cortex, but decreased FCS in the left middle frontal gyrus (accuracy, sensitivity and specificity, respectively: 87.3%, 73.5% and 100%) [55]; 3- increased global efficiency and resilience to targeted attack ($p < 0.05$), but

decreased clustering coefficient (brain functional networks; $p < 0.05$) [56]; 4- increased regional homogeneity (**ReHo**) in the right inferior frontal gyrus and the right putamen ($p < 0.005$; accuracy, sensitivity and specificity, respectively: 90.1%, 88.2% and 91.9%), but decreased ReHo in the left inferior temporal gyrus ($p < 0.005$) [57]; 5- decreased functional connectivity with nine clusters located at bilateral inferior temporal gyrus (**ITG**), bilateral transverse temporal gyrus of Heschl, left parahippocampal gyrus, right hippocampus, right thalamus, bilateral cerebellar Crus I/II and right posterior ITG ($p < 0.05$) [4]; and 6- decreased parameter of asymmetry in the left thalamus ($p = 0.001$; accuracy, sensitivity and specificity, respectively: 62.1%, 81.1% and 42.3%) [58].

Diffusion tensor imaging (DTI) and Diffusion-weighted imaging (DWI) assessments: Compared with control subjects,

Table 3: Below is a distribution of results from studies conducted since January 2015 on biomarkers among subjects at risk of psychosis before transition to psychosis, according to the type of biomarker, study design and group comparison.

Biomarkers					Group comparison			Trend in REP or REP+ subjects in the biomarker assessment comparison			
		Study design	Nbr. of studies	References	REP vs. CT	REP+ vs. REP-	REP vs. FEP	↑	↓	MuM of prediction	Non-significant differences
Brain	sMRI	FoU	4	[14,20,38,117]	[20,117]	[38]	[14]	[20,38]	[38]	[38]	[14,117]
		C-S	13	[6,39-45, 116,118–121]	[6,39-45, 116,118–121]		[41,43]	[41,42]	[39,40,43–45]		[6,43, 116, 118–121]
	fMRI	FoU	3	[46,47,51]	[46,47,51]			[46,47]	[46,47,51]		
		C-S	4	[48–50,122]	[48–50,122]			[48]	[48–50]		[122]
	rs-fMRI	C-S	8	[4,52–58]	[4,53–58]	[52,53]	[58]	[52,54–57]	[4,53–58]	[55,57,58]	[58]
	DTI	C-S	4	[59–61,63]	[59–61,63]			[59,63]	[59–61]		[59]
	DWI	C-S	1	[62]	[62]				[62]		
	EEG	FoU	7	[25,27, 28, 64, 65,69, 71]	[27,28, 64,65, 69,71]	[64]	[25]	[25,71]	[25,27, 28,64, 65,69, 71]		[64,65]
		C-S	11	[66–68,70, 72–74,123–126]	[66–68,70,72–74,123–126]			[72]	[66-68,70,72–74]		[123–126]
	MEG	C-S	1	[75]	[75]				[75]		
		FoU	1	[127]	[127]						[127]
	MRS	C-S	1	[77]	[77]			[77]			
	fNIRS	C-S	1	[31]	[31]					[31]	
	PET	C-S	2	[76,128]	[128]	[76]			[76]		[128]
	EMG	FoU	1	[32]	[32]						[32]
Blood	Inflammatory	C-S	2	[78,79]	[78]		[78,79]	[78,79]	[78]		[78]
	Fatty Acids	C-S	1	[81]	[81]			[81]	[81]		
	Hormonal	C-S	1	[82]	[82]			[82]			
	Aminoacids	C-S	1	[66]	[66]						[66]
	Enzymes	FoU	2	[80,83]	[80,83]		[80]	[80]	[83]		[80]
	Protein	FoU	1	[129]	[129]						[129]
Genetic	NRG1 mRNA	FoU	1	[85]		[85]		[85]			
	TSPO rs6971	C-S	1	[130]	[130]					[130]	
	PSRS	C-S	1	[86]			[86]	[86]			

Eyes	Oculomotor abnormalities	C-S	4	[87–89,131,132]	[87–89,131,132]	[87,88]		[87–89]			[87, 88, 131, 132]
	Retinal abnormality	C-S	1	[90]		[90]	[90]				
Others	Sleep (Actigraphy or sleep high density-EEG)	FoU	1	[91]	[91]		[91]				
		C-S	1	[92]	[92]		[92]				
	ORS	FoU	1	[36]	[36]				[36]		[36]
	Fecal samples	C-S	1	[77]	[77]	[77]	[77]				
	Urinary samples	C-S	1	[95]	[95]		[95]		[95]		
	ECG or photoplethysmography	C-S	2	[93,94]	[93,94]		[93]		[93]		[94]
	Immunoassays	C-S	1	[133]	[133]						[133]

REP subjects had: 1- higher radial diffusivity (p = 0.030) and trace (p = 0.031) in the cingulum bundle, but a lower fractional anisotropy (p = 0.028) [59]; 2- lower scores of the area under the rich-club curve, the mean strength of rich-club connections and local efficiency of the right accumbens (p = 0.012) [60]; 3- decreased forceps minor fractional anisotropy and superior longitudinal fasciculus radial diffusivity (p < 0.001) [61]; 4- decreased thalamo-orbitofrontal connectivity (p < 0.05) [62]; and 5- hemispheric asymmetric deficits of nodal efficiency, global and local efficiency (p < 0.05) [63].

Electroencephalogram (EEG) and Magnetoencephalography (MEG) assessments: Fujioka et al. [64] stratified REP subjects according to their remission: REPs^{+} (non- remitters) versus REPs^{-} (remitters, defined by a GAF score ≥ 61 and a score ≤ 2 on all SOPS positive subscales). At baseline, REP^{+} subjects showed smaller duration mismatch negativity (dMMN) amplitudes (p = 0.039).

With regard to control subjects, the REP subjects showed: 1- reduced dMMN amplitudes (p = 0.003 [64]; p = 0.02 [65]; p = 0.02 and d = 0.88 [66]; p between 0.005 and 0.018 [67]) and a difference in waveforms MMN (p < 0.05) [68]; 2- reduced 40 Hz auditory steady-state response (**ASSR;** p < 0.05 [68]; p = 0.04 and d = -0.72 [69]) and late-latency ASSRs (p = 0.02) [70]; 3- increased P50 ratio (p = 0.03), but decreased C-T difference (p= 0.009) [71]; 4- increased P300 inter-trial variability (p = 0.028) [72] and decreased P300 peak amplitudes (p = 0.024 [73]; p = 0.001 [72]); 5- reduced target P3b and novelty P3a amplitudes (p < 0.001; d = 0.37 [27]; p between 0.0002 and 0.006; d = 0.71 to 1.16 [28]); 6- reduced N100 adaptation (p = 0.001) [74]; and 7- decreased phase consistency of β/γ- band oscillations in visual cortex (p = 0.005; d = 0.63) [75].

Magnetic resonance spectroscopy (MRS), functional Near-infrared spectroscopy (fNIRS) and Position emission tomography (PET) assessments: Schifani et al. [76] stratified REP subjects according to their levels of stress-induced dopamine release in PFC: REPs^{+} (higher level) versus REPs^{-} (lower level). REPs^{+} had lower translocator protein (TSPO) expression in the hippocampus (p = 0.03).

Among 47 REP subjects, 82.4% and 70.2% were successfully classified using a modified Integral or a Centroid value from the Frontal Area, respectively [31]. Compared with control subjects, REP subjects were found to have increased levels of choline in anterior cingulate (p = 0.03) [77].

Blood biomarkers: Compared with another cohort of first-episode psychosis (**FEP**) subjects, REP subjects had: 1- lower homocysteine levels and higher methionine/homocysteine ratio (p = 0.016, whereas no differences were observed between REP and control subjects) [78]; 2- higher levels of immunoinflammatory analytes MCP-1, MIP-1β, TARC, BDNF, Eotaxin- 1 and IFN- γ (p < 0.001; same results were observed compared with control subjects) [79]; and 3- higher Ndel1 enzymes (p = 0.023; 52= 0.127, whereas no differences were observed between REP and control subjects) [80].

With regard to control subjects, REP subjects had: 1- lower levels of phosphatidylethanolamine and polyunsaturated fatty acids (eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid and Omega-3 index) and higher concentrations of sphingomyelin and nervonic acid (p < 0.0001) [81]; 2- increased levels of serum leptin (p= 0.025) [82]; and 3- lower circulating concentrations of arachidonylethanolamide (p = 0.003) and 2-arachidonoylglycerol (p < 0.001) [83].

Genetic biomarkers: Jagannath et al. [85] stratified REP subjects according to their long-term functioning levels: 98 REPs$^+$ (low level, i.e. GAF score ≤ 64) versus 31 REPs$^-$ (high level, i.e. GAF score ≥ 65). After a one-year follow-up, REPs$^+$ had higher pan-NRG1 mRNA (sensitivity= 73.3%; specificity = 57.7%). In REP subjects, the polygenic schizophrenia-related risk score was: 1- negatively associated with hippocampal volumes (p = 0.01) [86]; and 2- positively correlated with the hemispheric asymmetric deficits of local efficiency (p < 0.05) [63].

Eye biomarkers: Caldani et al. [87] stratified REP subjects according to their levels of neurological soft signs: REPs$^+$ (high level) versus REPs$^-$ (low level). Compared with control subjects, REPs$^+$ had more errors in the memory-guided saccades (p < 0.002) and more intrusive saccades (p < 0.005) [88]. Also in comparison with control subjects, REP subjects had higher antisaccade error rates (p < 0.001) [89].

Peredo et al. [90] found two clusters according to the REP subjects' retinal responses to luminance with the electroretinography (**ERG**), including: a first subgroup with alterations (54 REP$^+$) and a second with a control-like ERG profile (53 REP$^-$). Compared with REPs$^-$, REPs$^+$ were 2.7 more likely to present impaired cognitive function (p = 0.001).

Other types of biomarkers: He et al. [77] stratified REP subjects according to the definition of their risk of psychosis: REPs$^+$ (UHRs) versus REPs$^-$ (HR). REPs+ had increased levels of orders Clostridiales, Lactobacillales and Bacteroidales in fecal samples (p = 0.048; same results were observed compared with control subjects).

Compared with control subjects, REP subjects showed: 1- increased fragmented circadian rhythms and later onset of nocturnal rest (p = 0.04) [91]; 2- more wakefulness after sleep onset (p = 0.048; d = 0.63) and higher non-rapid eye movement sleep EEG power in the gamma band (p = 0.012; d = 0.816), observed in a large fronto-parieto-occipital area [92]; 3- decreased niacin skin sensitivity (**NS**; p < 0.05; when REP subjects were defined with attenuated symptoms, whereas no group differences were found between REP subjects defined with genetic risk and control subjects) [36]; 4- reduced variance of resting heart rate variability (**HRV**; p = 0.004; d = -0.74) and a reduced high-frequency power (p = 0.024; d = -0.64) during deep breathing [93]; however, Clamor et al. [94] found no differences in HRV; and 5- increase in biopyrrins and reduction of free immunoglobin light chains K and λ in urinary samples (p = 0.035) [95].

DISCUSSION

Since psychiatric diagnoses are mainly based on clinical observations and interviews, objective tests like biomarkers could be helpful to limit the duration of untreated prodromal symptoms [96]. Our main goal was to scope the literature to pin down biomarkers predictive of or associated with psychosis currently under study as reported since January 2015. We have mapped over 80 biomarkers which could have the potential to track early signs of SZ, which varied from brain imaging and genetics to proteins and retinal abnormalities.

We paid particular attention to the longitudinal studies that predicted transition of first-episode psychosis and to the effect sizes that characterized correlations between biomarkers and psychosis. Sample size, the length of longitudinal follow-ups and evidence of replication were also considered as important characteristics to highlight biomarkers. According to these criteria, a few studies stood out.

Thanks to a longitudinal study design, Koike et al. [31] found that frontal waveforms (fNIRS assessment) predicted 100% of the transition to psychosis of six particular REP subjects. This result could be the first evidence of the correlation between frontal waveforms and risks of transition, although previous studies had already related this biomarker to chronic patients [97]. Despite the small sample size used and the need for replication, fNIRS assessment offers the benefits of a small, non-invasive and low-noise instrument that is easy to carry around compared with other brain-imaging techniques. Similarly, salivary cortisol is a non-invasive biomarker that showed a 21.5-fold risk of transitioning to psychosis in a cohort of 417 REP subjects [37]; in fact, cortisol abnormalities had already been seen in SZ patients [98,99]. However, the study of hormonal changes represents a challenge, given the high inter-individual variability. In addition, auditory P300 event-related potential has been studied since the 1980s as a primary electrophysiological biomarker candidate for psychosis [100]. More recently, Higuchi et al. [24] and Hamilton et al. [27,28] contributed to enhancing the potential of P300 event-related responses or its subcomponent, the P3b, as biomarkers of transition to psychosis in 8, 73 and 15 REP-T subjects, respectively. Transition to psychosis was also predicted by reduced 40 Hz auditory steady-state responses (**ASSRs**) in 116 REP subjects among which 13 transitioned [30]. Reduced 40 Hz ASSRs were also observed in REP subjects compared with control subjects during two other studies assessed in this review [68,69].

Other biomarkers were found to clearly distinguish REP-T and REP-NT subjects. Higher brain transitivity was found to be strongly related to transition to psychosis when 16 subjects who transitioned were compared with 63 others who did not (Hedges g = 1.76) and with 44 control subjects (Hedges g = 1.41) [14]. Although studies before 2015 had already investigated brain networks in SZ patients [101–103] the Das et al. study [14] seems to be the first to relate brain transitivity to transition to psychosis. Similarly, decreased microstate D strongly differed between 20 REP-T and 34 REP-NT subjects (Cohen's d = -1.24) [25]. Bock et al. [25] were the first to assess microstates with respect to future transition to psychosis. Furthermore, the longitudinal decreased duration mismatch negativity (**dMMN)** amplitudes found in 11 REP-T subjects [26] seem promising. Since 2015, four other studies found decreased dMMN in REP subjects compared with control subjects [64-67].

Since 2015, no other clear replications of biomarkers to distinguish REP-T and REP-NT subjects were observed. However, some studies shared a similar purpose. For instance, subjects who transitioned had hypergyrification, i.e. higher levels of local gyrification index (**LGI**) in the left occipital region, compared with REP-NT subjects [20]. In contrast, other studies that compared subjects at risk with control subjects found hypogyrification (lower levels of LGI) in the lateral orbitofrontal, superior bank of the superior temporal sulcus, anterior isthmus of the

cingulate and temporal poles [39] and in the medial parieto-occipital and cingulate regions [40]. These opposite results could be explained by differences in the brain regions studied and the use of REP subjects disregarding who had transitioned. Previous investigations of gyrification in REP subjects suggested hypergyrification of frontal and parietal regions [104,105] with frontal hypergyrification associated with later development of a SZ spectrum disorder [106]. Gyrification parameters thus seem a promising avenue to predict transition.

As an alternative to follow-up studies, cluster analysis was proposed to identify subgroups of REP subjects according to a biomarker assessment (e.g., Peredo et al. [90]).The subgroups identified were then related to cognitive functioning, with the hypothesis that a low-functioning cluster would include subjects who will eventually transition to psychosis. Likewise, nine other studies have stratified REP subjects into subjects with high (REP^+) versus low deficits (REP^-; Table 3), in order to identify a biomarker related to the REP^+ state, assuming it would predict transition.

Most of the 96 studies assessed in this review had related a biomarker of interest to the state of being at risk compared with being a control subject, but not with transition to psychosis itself (78 studies in Table 3). Although such biomarkers still need to be further investigated in longitudinal design targeting REP-T subjects, these studies provided biomarker candidates, including mismatch negativity, 40 Hz ASSRs and P300 peak amplitude. These potential biomarkers have shown consistent differences between REP and control subjects in at least two independent cohorts assessed since 2015. However, there was a lack of consistency across studies assessing the same biomarker due to the wide range of instruments and measurements used.

CLINICAL USE

Early treatment is known to improve the prognosis of SZ spectrum disorders by reducing the severity of symptoms and improving long-term functioning [107–109]. Hence, in the last version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, 2013), researchers attempted to add biomarkers as external validations to enhance diagnoses [110]. This idea was apparently premature, as biomarkers are not featured in DSM-5 [18]. Still, the keen interest in biomarkers in the last decade has stimulated research on biological assessments likely to monitor the development of a psychiatric disorder in the same way that mammography serves to monitor breast cancer [111]. Reliable, reproducible and non-invasive biomarkers would help to inform clinical guidelines on how and when to provide care to subjects slipping into psychosis. Several biomarkers are currently under study for this very purpose. From this perspective, biomarkers could be useful in walk-in clinics [112] where, for instance, young people seek various health and wellness services, before diagnosis of psychiatric illness. However, further research needs to better understand the stages in the progression of psychotic disorders, in order for biomarkers to be adequately integrated into follow-up processes provided to young individuals in need of care.

LIMITATIONS

We limited the scope of our review to studies conducted since January 2015 to identify biomarkers being currently investigated, although it cannot be excluded that an earlier study could eventually provide a relevant biomarker. In this review, we also included studies with variegated definitions of REP subjects (genetic and/or clinical susceptibilities). Assessing genetic and clinical risks combined can be unadvisable, considering that they are not based on the same concept of risk. Our review also highlighted the difficulty of clearly identifying an individual's age at which a given biomarker was assessed and, hence, if it truly revealed major neurodevelopmental changes in the individual's brain during the lead time to the onset of psychosis. Lastly, we limited this review to assessing the risk of SZ spectrum disorders, although first-episode psychosis could also lead to bipolar disorder [113,114].

CONCLUSION

Several parameters need to be considered to assess the relevance of a biomarker, including: ease of use, cost/benefit ratio, level of intrusiveness, accuracy of prognostics, and replication and consistency across studies. No biomarker of psychosis has clearly met all these criteria as of yet, but research is in progress. By this review, we aim to inform practitioners in the field that several promising candidates have been identified in order to eventually be able to track psychosis and SZ spectrum disorders. Also, given that a number of causal mechanisms for psychiatric disorders have been acknowledged [115] and that heterogeneity and comorbidity are part of the portrait, several biomarkers may be needed and, perhaps, combined to determine the development of psychosis in individuals. Moreover, all biomarkers currently under investigation can be promising in a specific developmental stage. While further research still needs to assess the when and where of a biomarker, studies in the field are promising and the translational clinical benefits are about to be revealed.

DECLARATION OF COMPETING INTERESTS

The authors hereby declare that they have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

CONFLICTS OF INTEREST

C. Mérette, Professor at Université Laval is listed as co-inventor in a patent application (Appl. No.: 16/685960) entitled "Use of electroretinography (ERG) for the assessment of psychiatric disorders" and holds shares in a start-up company (diaMentis), which owns a license from Université Laval to further develop and market the claims listed in the patent application. A. Painchaud reported no biomedical financial interests or potential conflicts of interest. R. Peredo Nunez De Arco reported no biomedical financial interests or potential conflicts of interest. P. Marquet reported no biomedical financial interests or potential conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of the Canadian Institutes of Health Research funding bodies.

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Cite this article

Painchaud A, Peredo R, Mérette C, Marquet P (2022) How can we Track Psychosis? A Scoping Review of Biomarkers of Transition in Subjects at Risk. JSM Biomar 5(1): 1014.