

Decisional Capacity for Informed Consent in Schizophrenia Research

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Background: The adequacy of subjects' informed consent to research is the focus of an important public and professional debate. The potential impairment of decisional capacity in persons with schizophrenia is central to the discussions. This study ascertains the decisional capacity for informed consent in schizophrenic research subjects, to determine if reduced capacity relates to specific aspects of psychopathologic features and to test the hypothesis that reduced capacity can be remediated with an educational informed consent process.

Methods: Decisional capacity was assessed for 30 research subjects with schizophrenia and 24 nonill (normal) comparison subjects. Measures of psychopathologic features and cognition were obtained for the subjects with schizophrenia. Subjects who performed poorly on the decisional capacity measure received an educational intervention designed to

improve their ability to provide informed consent and were then retested.

Results: The patient group did not perform as well as the controls on initial decisional capacity assessment. Poor performance was modestly related to the extent of symptoms but robustly related to cognitive impairments. Following the educational intervention, the performance of subjects with schizophrenia was equal to that of the nonill comparison group.

Conclusions: Many persons with schizophrenia may be challenged by the cognitive demands of an informed consent process for research participation. In many cases, their reduced capacity can be compensated by a more intensive educational intervention as part of the informed consent process.

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THE DECISIONAL capacity of persons with schizophrenia has become central to the debate on the ethics of psychiatric research.¹⁻³

Schizophrenia is manifested by distortions in perception, disorganization of thought, and weakening of motivation and emotional responsivity.⁴ Any of these elements of the illness, in theory, may reduce the capacity to make decisions. Commentators in the media, perhaps influenced by the public caricature of persons with schizophrenia as being bizarre and "out of

touch," have questioned whether persons with schizophrenia can make informed judgments about participating in research. It is urgent to address this issue with relevant data, as state and national commissions are proposing statutes and regulations to address perceived problems in the conduct of research with sub-

jects whose diagnoses are associated with decisional impairments.⁵⁻⁷ Most patients with schizophrenia, however, are not judged to be incompetent and routinely handle their day-to-day affairs. Studies^{8,9} of the capacity of schizophrenic patients to make decisions regarding their treatment demonstrate that, as a group, they do more poorly than nonill (normal) comparison subjects and other patient groups with medical and psychiatric illnesses. However, numerous people with schizophrenia, even when acutely ill, perform no worse than many members of the general population.^{8,9} Recent data¹⁰ suggest that patients with schizophrenia participating in research are able to understand and retain consent information.

This study was designed to shed light on this issue by examining the performance of a group of schizophrenic research subjects. The aims were to (1) assess the degree of decisional impairment in a cohort of research subjects, (2) evaluate the extent to which the symptoms of schizophrenia and cognitive impairments affect

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SUBJECTS AND METHODS

SUBJECTS

Schizophrenic subjects were drawn from inpatient and outpatient research programs at the Maryland Psychiatric Research Center (MPRC), Baltimore. Twenty inpatients and 10 outpatients meeting *DSM-III*¹¹ or *DSM-IV*¹² criteria for schizophrenia ($n = 28$) or schizoaffective disorder ($n = 2$) were selected for the study if they were enrolled as research subjects and receiving clinical services in an inpatient research unit for treatment-resistant schizophrenia ($n = 10$), an inpatient research unit focused on young schizophrenic patients with chronic illnesses ($n = 10$), or an outpatient research program focused on patients whose schizophrenia is only partially responsive to treatment ($n = 10$). Patients were eligible for selection if they were in a research protocol or if they had signed a consent form preparatory for research participation. Inpatient subjects were selected in order of date of signing a consent form (most recent first). Twenty-two were approached; 20 assented. For eligible outpatients, selection depended on the time of the next appointment. Ten patients were approached, and 10 assented. Medication status was not a selection criterion, but all subjects were receiving antipsychotic medication during participation in this study. Approximately half the patients were taking new-generation compounds; exact data are unavailable as the code on clinical trial participants has not been broken. Drug treatment was in a continuation phase in all patients, and minimal clinical change was expected between assessment sessions. For 7 patients taking clozapine, the dose range was from 400 to 700 mg/d, with a modal dose of 400 mg/d. The dose range for haloperidol was from 10 to 30 mg/d, and for olanzapine, from 10 to 30 mg/d, with 15 mg/d being the modal dose for each. Univariate statistics (the 2×2 Yates corrected χ^2 test for discrete and the 2-group t test for continuous variables) were used to compare this sample with the entire patient subject population of the MPRC–National Institute of Mental Health Intervention Research Center ($N = 493$) to determine representativeness.

The nonill comparison subjects were recruited from community centers and a free medical clinic by researchers at the University of Virginia, Charlottesville. They were told that the study would evaluate how people use information to make decisions and that no treatment would be provided. Descriptive information for the 30 schizophrenic subjects and the 24 normal subjects is provided in **Table 1**.

In accordance with a federal regulation (45 CFR §46.101.B), this protocol was reviewed and determined exempt from written informed consent by the University of Maryland, Baltimore, Institutional Review Board. Patients were enrolled in the study after the nature of their requested involvement was described to them and they assented to participate.

CLINICAL RATINGS

Clinical assessments were conducted through the support framework of the MPRC–National Institute of Mental Health Clinical Research Center. The *DSM-IV* diagnosis is made

as a best estimate by a trained research psychiatrist using all available sources of information, including the Structured Clinical Interview for the *DSM*, family informants, and medical records. The Brief Psychiatric Rating Scale (BPRS)¹³ is routinely administered in each program to measure psychopathologic features. Brief Psychiatric Rating Scale evaluations were always within a week of testing for decisional capacity. Raters are typically research nurses or master's level clinicians trained to reliability standards by the MPRC–National Institute of Mental Health Intervention Research Center Assessment Core. Pearson product moment correlations were performed to ascertain the relation between schizophrenia symptoms, as measured by the BPRS, and performance on The MacArthur Competence Assessment Tool–Clinical Research (MacCAT-CR).

ASSESSMENT OF DECISIONAL CAPACITY

Decisional capacity was measured by the MacCAT-CR. This instrument provides a structured format for the assessment of 4 areas of decisional capacity related to generally applied legal standards for competence to consent to treatment and research: understanding relevant information, appreciation of the implications of the information for one's own situation, reasoning with the information in a decisional process, and evidencing a choice.¹⁴ It is derived from an instrument developed to measure capacity to consent to treatment in the clinical setting, The MacArthur Competence Assessment Tool–Treatment,¹⁵ which, in turn, represents a condensation of an extensive set of instruments constructed for research on informed consent and decisional capacity.¹⁶ Both sets of instruments have demonstrated good inter-rater reliability and concurrent validity as capacity assessment tools.^{8,9,16} Many issues may compromise capacity to consent, including hope, unrealistic expectations, relations, and various emotions. However, the impact of these affective factors is expected to be manifest in the 4 areas of decisional capacity.¹⁷

We developed a version of the MacCAT-CR that describes a randomized, double-blind trial of a novel antipsychotic medication for this study. Subjects were told to pretend that they were being asked to consent to participation in the study. Information disclosure was followed by structured queries and probes of the 4 areas of decisional capacity previously described. A scoring manual provided explicit criteria for raters, with possible scores ranging from 0 to 6 on the Understanding scale, 0 to 6 on the Appreciation scale, 0 to 8 on the Reasoning scale, and 0 to 2 on the Choice scale. (The manual for the MacCAT-CR and the version used in this study are available from the authors.) Ten raters were trained to administer the MacCAT-CR. Reliability exercises were conducted involving 10 raters and 12 patients, with raters alternating as testers and observers. The version of the MacCAT-CR developed for this study was evaluated for reliability with intraclass r statistics for continuous, and a weighted κ for dichotomous, ratings.¹⁸

To provide similar decisional capacity data drawn from a nonill population, one of us (J.K.) administered a version of the MacCAT-CR identical in form but slightly different in content to subjects recruited for a separate study

at the University of Virginia. Both versions were based on a hypothetical clinical trial. The minor differences involved naming the drug and overlapping, rather than an identical list of, adverse effects.

COGNITIVE ASSESSMENT

Subjects completed a brief cognitive battery to assess overall level of cognitive impairment and abilities that are relevant to the process of obtaining informed consent. The battery included the following: (1) the Wide Range Achievement Test 3 reading subtest, a measure of single-word decoding¹⁹; (2) the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a brief screening measure that yields scaled index scores for immediate and delayed memory, language, attention, and visuospatial skills, and an overall total scaled score²⁰; and (3) the letter-number sequencing subtest from the Wechsler Adult Intelligence Scale III, a measure of auditory working memory.²¹ The Wide Range Achievement Test and the RBANS have a normal mean of 100 and an SD of 15 based on the normal standardization samples described in test manuals. Letter-number sequencing has a normal mean of 10 and an SD of 3 based on the Wechsler Adult Intelligence Scale III standardization sample. Patients also received a nonstandard version of the Gray Oral Reading Test.²² The test was adapted so that subjects read aloud a series of 7 short passages and then answered 5 questions that tested their comprehension of the material. The standard version of the test includes a total of 13 items. The items selected for this study were drawn from the easy and moderate difficulty levels of the 2 test forms.

Testing was performed within 7 days of the MacCAT-CR assessment. Complete test protocols were completed by 26 of the 30 subjects. One subject was not tested; 3 were missing single measures, as they wanted to discontinue testing or had difficulty with task demands, producing data that were judged to be invalid. All cognitive tests were administered by a single research assistant trained and supervised by one of us (J.M.G.) in the MPRC–National Institute of Mental Health Intervention Research Center Neurocognitive Core.

To assess the relation between the MacCAT-CR score and cognitive variables, we performed stepwise regressions for the Understanding, Appreciation, and Reasoning scales, with all cognitive variables available for entry at the first step.

EDUCATIONAL REMEDIATION OF DECISIONAL IMPAIRMENTS

The poor performance of the subjects with schizophrenia on the MacCAT-CR, which assessed their capacities in relation to a hypothetical study, contrasted sharply with the impressions of research staff that these same subjects previously had given adequate consent for participation in actual research projects. These impressions, moreover, were confirmed by a standardized measure of understanding, the Evaluation of Signed Consent (ESC),²³ which each of them had been required to pass before enrollment into an actual study. It was hypothesized that the extended educational process that

preceded consent to the actual study accounted for the difference.

A subset of poorly performing schizophrenic subjects participated in an educational process during a 1-week period in which information about the MacCAT-CR hypothetical study was presented. *Poor performance* was defined as a score below 20, the normal control median, on the MacCAT-CR Understanding scale. This cutoff point was chosen to allow room for improvement in performance and because scores above the cutoff point are unequivocally normal. All but 2 of the patients who scored below the normal control median were available for this part of the study ($n = 20$). The 2 patients had scored 19 and 6 on the Understanding scale; 1 declined further participation, and 1 was medically ill.

The educational remediation intervention was an abbreviated version of the informed consent process used at the MPRC. Subjects took part in 2 sessions of about 30 minutes reviewing the study protocol. Information was provided again, questions were asked, and prompts were used to assist the subjects in mastering the material. Some inpatient subjects also spent extra time with a computerized interactive routine designed to teach basic concepts such as protocol, random assignment, drug withdrawal, and placebo. Others spent some extra time with a flip chart that reviewed relevant information. Personnel were from the nursing or research staffs of each clinical unit and were accustomed to assisting patients with informed consent. The outpatient subjects had only the 2 intervention sessions without additional aids.

STATISTICAL ANALYSIS

Basic univariate statistics, the 2-group t test for continuous variables, and the Yates corrected $2 \times 2 \chi^2$ test for discrete variables were used for comparing demographic characteristics of the schizophrenic subjects with a schizophrenic reference group. To examine the capacity for informed consent in schizophrenic research subjects compared with nonill comparison subjects, the 2-group t test was used. To test the hypothesis that reduced capacity for informed consent can be remediated with an educational informed consent process, the paired t test was used to compare preeducation vs posteducation decisional capacity scores. The Pearson product moment correlation was used, assessing the association between decisional capacity and cognitive measures.

For the 2-group comparison between 30 patients with schizophrenia and 24 normal comparison subjects, there was 80% statistical power, with a type I error of 5% to detect a difference of 5.45 Understanding units, 1.83 Reasoning units, 1.44 Appreciation units, and 0.45 Choice units, each with an effect size of 0.8. Actual results, with the exception of Choice, exceed these limits and effect size of 0.8.

For the paired t comparison between pretest and posttest scores of 20 patients with schizophrenia, we have 80% statistical power, with a type I error of 5% to detect a difference of 3.9 Understanding units, 1.8 Reasoning units, and 1.4 Appreciation units, each with an effect size of 0.66. Actual results, with the exception of Reasoning, exceed these limits and effect size of 0.66.

Table 1. Demographic Characteristics of Schizophrenic Subjects and Nonill Comparison Subjects*

Characteristic	Schizophrenic Subjects (n = 30)	Normal Control Subjects (n = 24)	Schizophrenic Reference Group (N = 493)	Test Statistic†	P
Females, %	43.3	21.8	32.9	$\chi^2_1 = 0.96$.33
Nonwhites, %	23.3	29.2	31.6	$\chi^2_1 = 0.56$.45
Age, y	40.2 (8.8)	39.7 (10.2)	34.5 (8.9)	$t_{521} = 3.41$.001
Education, y	12.2 (2.4)	11.5 (2.1)	12.1 (2.3)	$t_{521} = 0.21$.82
Length of illness, y	20.0 (7.9)	...	14.2 (8.3)	$t_{521} = 3.72$.001
Hollingshead socioeconomic status score	3.9 (2.7)	4.3 (1.0)	4.1 (1.0)	$t_{521} = 0.92$.36

*Data are given as mean (SD) unless otherwise indicated. Ellipses indicate data not applicable.

†Comparison of the schizophrenic subjects with the schizophrenic reference group.

Table 2. MacCAT-CR Scores for Subjects With Schizophrenia and the University of Virginia Nonill Comparison Group*

MacCAT-CR Scale	Theoretical Range of the Variable	Schizophrenic Subjects (n = 30)	Normal Control Subjects (n = 24)	t_{52}	P
Understanding	0-26	12.9 (8.5)	20.2 (3.8)	3.90	.001
Reasoning	0-8	3.5 (2.8)	5.5 (1.4)	3.20	.002
Appreciation	0-6	2.3 (2.0)	4.4 (1.5)	4.30	<.001
Choice	0-2	1.6 (0.7)	1.9 (0.3)	1.96	.06

*Data are given as mean (SD) unless otherwise indicated. MacCAT-CR indicates The MacArthur Competence Assessment Tool—Clinical Research.

Table 3. MacCAT-CR Pearson Product Moment Correlations With Symptoms for the 30 Schizophrenic Subjects*

MacCAT-CR Scale	Total BPRS Score	P	BPRS Factor 1†	P
Understanding	-0.34	.07	-0.38	.04
Reasoning	-0.47	.01	-0.52	.01
Appreciation	-0.27	.15	-0.37	.04
Choice	-0.16	.40	-0.31	.10

*MacCAT-CR indicates The MacArthur Competence Assessment Tool—Clinical Research; BPRS, Brief Psychiatric Rating Scale.

†Psychosis factor.

decisional capacity, and (3) explore the efficacy of an educational intervention to improve the decision-making capacity of impaired subjects.

RESULTS

The present study cohort was mildly more symptomatic on BPRS measures when compared with MPRC patients as a whole (mean [SD] BPRS score, 47.3 [13.9] vs 39.6 [12.5]; $t_{492} = 3.22$; $P = .001$). The mean (SD) BPRS factor 1 psychosis score was also significantly higher in the present study cohort (10.6 [4.2] vs 8.8 [4.3]; $t_{491} = 2.14$; $P = .03$). This study cohort, although skewed toward chronic schizophrenia with substantial psychosis that has proved resistant to ordinary treatment, is representative of the patients who participate in studies at the MPRC on sociodemographic and illness chronicity variables.

Reliability results for 3 of the essential elements of informed consent reflect substantial between-rater agreement on the scoring of items. The weighted κ for Choice (yes or no) was 0.52 and represents 82% agreement between raters. The Understanding scale had an intraclass

correlation of 0.98. The intraclass correlation was 0.84 for the Reasoning and Appreciation scales.

MacArthur Competence Assessment Tool—Clinical Research scores for the 30 subjects with schizophrenia and the 24 members of the normal comparison group at the University of Virginia are presented in **Table 2**. The subjects with schizophrenia scored significantly lower than the comparison group on the Understanding, Reasoning, and Appreciation scales; scores on the Choice scale were lower as well but just failed to reach statistical significance.

SYMPTOMS AND DECISIONAL CAPACITY

Pearson product moment correlations with total BPRS scores, representing global pathologic characteristics, and factor 1 scores, representing psychosis, are presented in **Table 3**. Psychopathologic features showed a moderate negative correlation with performance, reaching statistical significance for the Understanding and Reasoning scales.

COGNITION AND DECISIONAL CAPACITY

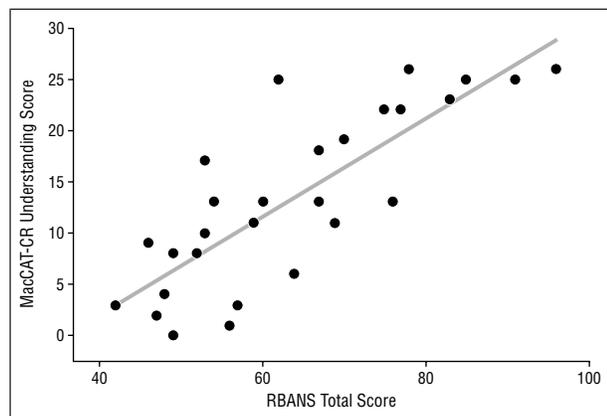
The patients had a mean standard score of 82.2 (SD, 16.2) on the Wide Range Achievement Test 3 (normal mean, 100; SD, 15), a scaled score of 5.5 (SD, 3.2) on letter-number sequencing (normal mean, 10; SD, 3), and an RBANS total scaled score of 63.3 (SD, 14.4; normal mean, 100; SD, 15). Thus, this is a sample with marked impairments that might be expected to compromise decisional capacity.

There were 2 significant predictors of Understanding scale performance: the RBANS total score, $R^2 = 0.67$ ($P < .001$) (**Figure**); and the Gray Oral Reading Test word reading score, $R^2 = 0.09$ ($P < .006$). There were 2 significant predictors of the MacCAT-CR Reasoning scale: the

RBANS total score, $R^2 = 0.58$ ($P < .01$); and the RBANS immediate memory index, $R^2 = 0.09$ ($P < .02$). Two significant predictors were observed for the Appreciation scale: letter-number sequencing, $R^2 = 0.66$ ($P < .02$); and the Visuospatial scale from the RBANS, $R^2 = 0.06$ ($P < .03$). Therefore, cognitive measures were highly predictive of MacCAT-CR performance.

As shown in **Table 4**, the 20 subjects who completed the MacCAT-CR a second time after the educational intervention showed significant improvements in Understanding scores. Only 9 of the 20 patients still scored below the cutoff of 20, bringing the total number of subjects with schizophrenia who scored 20 or higher either at the original administration of the MacCAT-CR or after remediation to 21 of 30. This proportion of subjects (70%) was significantly greater than the proportion of normal comparison subjects in the University of Virginia study who scored 20 or higher (46%; $P < .04$). Moreover, there was no difference in the mean Understanding scores between these two groups (19.3 [SD, 7.1] for the schizophrenic group [$n = 21$] vs 20.2 [SD, 3.8] for the normal subjects [$n = 24$]; $t_{43} = -0.54$; $P = .59$).

The MacCAT-CR does not provide a score below which a subject is known to lack capacity for informed consent. However, 2 patients continued to score below the range defined by the normal control group after the educational intervention. The lowest-scoring subject was removed from research participation based on lack of capacity independent of this study. The other patient continued in research and had passed the ESC test at the time



The Pearson product moment correlation between decisional capacity and cognitive performance ($r = 0.82$). MacCAT-CR indicates The MacArthur Competence Assessment Tool—Clinical Research; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

consent was accepted as valid. In earlier work,²³ some subjects required more than the 1 week of educational intervention to pass the ESC. This may account for continued research participation despite a low score on the second MacCAT-CR.

COMMENT

Patients with schizophrenia demonstrated significantly poorer performance than a nonill comparison group on the MacCAT-CR, an instrument designed to measure decisional capacities relevant to consent to research. Performance was only moderately related to psychotic symptoms per se, but was strongly correlated with cognitive impairments. These findings agree with the common clinical observation that the degree of psychotic symptoms, except at the extreme, does not robustly predict patients' functionality in daily life.²⁴

The poor performance of many of the subjects with schizophrenia, however, did not reflect an enduring inability to understand the information relevant to a research study. When offered additional opportunities to learn the necessary data, most subjects who scored below an a priori cutoff were able to bring their scores into the range of a comparison group of people without schizophrenia. This suggests that people with severe forms of schizophrenia may be able to give informed consent for research, although a single-session brief presentation of research procedures may not be sufficient. Rather, an informed consent process that engages potential subjects over time and is sensitive to the negative impact of cognitive impairment may be essential for adequate informed consent. This conclusion is also supported by the report¹⁰ of good performance by schizophrenic subjects on informed consent material after learning and practice sessions.

This study also underscores the proper role of capacity assessment instruments like the MacCAT-CR. Such instruments can identify subjects at high risk for impaired performance in an actual informed consent process, and many of these subjects can provide adequate consent following an educational intervention. Therefore, poor performance on a decisional capacity assessment should not exclude subjects from research participation. Needed instead are efforts to identify the basis for the observed impairments and to devise means of attempted remediation.

Although these findings offer hope regarding the decisional capacity of schizophrenic patients, they derive from a limited number of subjects in a single institution and are viewed as preliminary. The results are sup-

Table 4. Results of the 20 MPRC Patients With a Baseline Understanding Scale Score of Less Than 20 Who Completed the Education Program*

MacCAT-CR Scale	Theoretical Range of the Variable	Preprogram Score	Postprogram Score	Change in Score	Paired t_{19}	P
Understanding	0-26	8.35 (5.4)	18.35 (7.3)	10.00 (5.9)	7.55	.001
Reasoning	0-8	2.35 (2.0)	3.70 (2.9)	1.35 (2.7)	2.21	.04
Appreciation	0-6	1.35 (1.3)	3.25 (2.4)	1.90 (2.1)	3.95	.001

*Data are given as mean (SD) unless otherwise indicated. MPRC indicates Maryland Psychiatric Research Center; MacCAT-CR, The MacArthur Competence Assessment Tool—Clinical Research.

ported by experience at the MPRC with the ESC test, which documents that patients can achieve a good understanding of protocol risks, demands, and procedures for withdrawing from a study and other data relevant to informed consent. Similar results reported from the University of California, Los Angeles,¹⁰ also suggest that these results may generalize more broadly to research subjects with schizophrenia. Nevertheless, additional work will be required to determine the generalizability of these data to other samples, diagnostic groups, and research settings and to identify the most effective means of educating research subjects to diminish the effects of their cognitive limitations. The question of how to use decisional capacity data from normal populations to define the range of performance that constitutes "competence" for informed consent is not resolved. This study is also limited in this regard by using a normal comparison group developed at a different site.

Successful remediation through an educational informed consent process has clear implications for the validity of consent at the time it is given. A complicated and unresolved issue relates to perseverance over time of understanding, appreciation, reasoning, and choice. Experience with the ESC suggests surprisingly good retention over time and following medication withdrawal.²³ We do not have data with the MacCAT-CR in a schizophrenic sample to address this question, but data from a group of depressed subjects showed little change in performance over time.²⁵ Nevertheless, we suggest that retention of key elements, rather than detailed knowledge, is critical during research participation. Key elements certainly include awareness that one is in a research study, that participation is voluntary, and that withdrawal of consent can be done without a penalty. Remembering the name of a drug or the full list of adverse effects may be less important in determining an ethical basis for continued research participation.

Concerning the public discussion of decisional capacity of the mentally ill to consent to research, we call attention to 3 implications of the data reported. First, patients with schizophrenia who have chronic and severe illnesses may have decisional capacity for informed consent. Second, if decisional capacity is impaired, it may be remediated. Third, cognition appears more relevant than psychosis in predicting decisional capacity in schizophrenic patients. It follows that the proposition that a psychotic person ipso facto should lose decision-making power for research decisions is flawed and stigmatizing. Rather than restrict research participation for categories of patients, emphasis should be placed on assuring that procedures for informing and documenting adequacy of consent are routinely practiced.

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