ABSTRACT
This paper provides a brief review of commonly used statistical methods for analyses of ordinal response data. Generalized CMH Score Tests of Marginal Homogeneity, GEE, and random-intercepts logistic regression ordinal model for analysis of repeated ordinal response data will be particularly discussed. SAS procedures, Proc NLMIXED, Proc GENMOD, Proc IML, and Proc FREQ for categorical ordinal analysis, are described and illustrated with data from a clinical trial. A SAS macro to produce estimated marginal Probabilities will be presented.

INTRODUCTION
Ordinal variables are common in clinical research studies. Ordinal variables have a hierarchical ordering, such as Severity score (none, mild, moderate, severe). Repeated measures refer to multiple measurements taken from the experimental unit over time. For example, many clinical studies require patients to return to the clinic at several times and observe the response variable at each visit. The layout for the sample data with two treatments is shown in the following:

<table>
<thead>
<tr>
<th>PATINET</th>
<th>TREATMENT</th>
<th>VISIT</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>A</td>
<td>1</td>
<td>y_{111}</td>
<td>y_{112}</td>
<td>y_{113}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1001</td>
<td>B</td>
<td>1</td>
<td>y_{211}</td>
<td>y_{212}</td>
<td>y_{213}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

These longitudinally repeated measures can be used to characterize a response profile over time. Repeated measures within a subject are usually positively correlated. The correlation structure of the longitudinal data can be described by random subject effects. Random subject effects indicate the degree of subject variation that exists in the population of subjects. Data from studies with repeated measurement in general are incomplete due to drop out. We will use terminology of little and Rubin (1987, Chapter 6) for the missing-value process. A non-response process is said to be missing completely a random (MCAR) if the missing is independent of both unobserved and observed data and missing at random (MAR) if, conditional on the observed data, the missing is independent of the unobserved measurements. When either of these is plausible, with a likelihood-based analysis it is not necessary to model the missingness mechanism (Agresti A. 2002).

For ordinal response data, we can compare mean response score between treatments by assigning numerically score which are the ranks of the categories when ordered from smallest to largest. This continuous model does not take into account the ceiling and floor effects of the ordinal outcome. The result can be biased when the ordinal variable is highly skewed. Here we first use a generalized CMH test for testing marginal homogeneity at the end of the study. Next, we use the GEE method implemented in the GENMOD procedure to fit a marginal model. The mean response of the marginal model depends only on covariates variable, and not on random effects. GEE uses quasi-likelihood estimation and assumes that the missing data are MCAR. To accommodate random effects, we describe a mixed-effects proportional odds model using the NLMIXED procedure. The NLMIXED procedure relies on approximating the marginal log likelihood by integral approximation through Gaussian quadrature. The objective function for the NLMIXED procedure is the marginal log likelihood obtained by integrating out the random effects from the joint distribution of responses and random effects using quadrature techniques. Although these are very accurate, the number of random effects that can be practically managed is limited (SAS/STAT). Since the estimation of model parameters is based on Maximum likelihood approach, the missing data are assumed to be MAR.
COCHRAN-MANTEL-HAENSZEL STATISTICS
We can use Cochran-Mantel-Haenszel Statistics to test ‘General Association’ between the Treatment and Response variables at the end of the study. The null hypothesis is that there is no association between the Treatment and Response variables at the end of the study. The alternative hypothesis is that the distribution over response categories differs among treatment levels.

Cochran-Mantel-Haenszel Statistics can be obtained in SAS using the CMH option in FREQ procedure.

```sas
PROC FREQ DATA=CHISQDB;
   TABLE TREATMENT*HAMD01/CMH CHISQ TREND NOPERCENT NOCOL;
RUN;
```

Summary Statistics for treatment by HAMD01

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Alternative Hypothesis</th>
<th>DF</th>
<th>Value</th>
<th>Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonzero Correlation</td>
<td>1</td>
<td>4.4038</td>
<td>0.0359</td>
</tr>
<tr>
<td>2</td>
<td>Row Mean Scores Differ</td>
<td>1</td>
<td>4.4038</td>
<td>0.0359</td>
</tr>
<tr>
<td>3</td>
<td>General Association</td>
<td>3</td>
<td>5.9155</td>
<td>0.1158</td>
</tr>
</tbody>
</table>

From the above output, we see that the test for general association is non-significant (p=0.1158), which indicates a lack of evidence of rejecting null hypothesis.

GENERALIZED ESTIMATING EQUATIONS (GEE)
GEE was introduced by Liang and Zeger (1986) as a method of parameter estimation for correlated data. It is a common choice for marginal modeling of ordinal response if one is interested in the regression parameters rather than variance-covariance structure of the longitudinal data. The covariance structure of GEE is regarded as nuisance. In this regard, the estimators of the regression coefficients and their standard errors based on GEE are consistent even with mis-specification of the covariance structure for the data.

Let \( Y_{ij} \), \( i = 1, \ldots, n \), \( j = 1, \ldots, T \) be the \( j \) th outcome for \( i \) th subject, where we assume that observations between different subjects are independent and outcomes observed within the same subject are correlated. First, we specify a marginal model

\[
g(E[Y_{ij}]) = x_{ij} \beta
\]

Where \( x_{ij} \) is a \( p \times 1 \) vector of covariates for the \( j \) th outcome for \( i \) th subject, \( \beta \) is the regression parameters of interest, link function \( g(.) \) converts the expected value \( \mu \) of the response variable to the linear predictor.

Additionally, we need to specify an assumed covariance structure for the correlated data. The working variance-covariance matrix for \( y_i \) is model as

\[
V_i = \phi A_i^{1/2} R(a) A_i^{1/2},
\]

Where \( A_i \) is the \( n \times n \) diagonal matrix of variance function \( V(\mu_i) \), \( R(a) \) is the \( n \times n \) working correlation matrix of longitudinal explanatory variable values for \( i \) subject. Common working correlation forms include independence, exchangeable, unstructured, AR(1), M-dependent and Fixed (See Diggle 1994 for detail). For multinomial response data, independence is currently the only working correlation matrix in SAS. \( R_i(\alpha) \) of independence structure is a \( n \times n \) identity matrix. It indicates that the longitudinal data are not correlated.

The GEE estimator of \( \beta \) is the solution of
Let $R_j(x) = \Pr(Y \leq j)$ denote the cumulative probability of the $j$th or lower response category, then the odds ratio comparing $x_A$ to $x_B$ is as follows:

$$\frac{R_j(x_A)/(1 - R_j(x_A))}{R_j(x_B)/(1 - R_j(x_B))} = \exp[(x_A - x_B)' \beta]$$

One interest is to assess the difference in rating for the two treatments. The GEE marginal model is specified in the form:

$$\log[P(Y \leq j)] = \alpha_j + \beta_i \times \text{Treatment} + \beta_2 \times \text{Visit} + \beta_3 \times \text{Treatment} \times \text{Visit}$$

SAS GENMOD PROCEDURE

The GENMOD procedure can fit marginal models to correlated longitudinal data by the GEE method.

```sas
PROC GENMOD DATA=ORDDB;
   CLASS PATIENT TREATMENT VISIT;
   MODEL HAMD01=TREATMENT VISIT TREATMENT*VISIT/DIST=MULTINOMIAL LINK=CLOGIT TYPE1 AGGREGATE=TREATMENT;
   REPEATED SUBJECT=PATIENT/TYPE=IND;
   ESTIMATE 'LogOR12' TREATMENT -1 1 / EXP;
RUN;
```

The AGGREGATE=TREATMENT option in the MODEL statement specifies the variable TREATMENT as defining multinomial populations for computing deviances and Pearson chi-squares. By default, the response is sorted in increasing ASCII order. It is important to check the "Response Profiles" table to verify that response levels are appropriately ordered. The TYPE=IND option in the REPEATED statement specify working correlation structure as independence. The ESTIMATE statement compute log odds ratios of one treatment group over the other. The EXP option in the ESTIMATE statement exponentiates the log odds ratios to form odds ratio estimates.

### Analysis Of GEE Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>95% Confidence Limits</th>
<th>Z</th>
<th>Pr &gt;</th>
<th>Z</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept1</td>
<td>0.7412</td>
<td>0.1479</td>
<td>0.4513 - 1.0310</td>
<td>5.01</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept2</td>
<td>2.1141</td>
<td>0.1662</td>
<td>1.7884 - 2.4399</td>
<td>12.72</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept3</td>
<td>5.3356</td>
<td>0.3189</td>
<td>4.7105 - 5.9606</td>
<td>16.73</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment 0</td>
<td>-0.6123</td>
<td>0.2397</td>
<td>-1.0821 - -0.1425</td>
<td>-2.55</td>
<td>0.0106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment 1</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000 - 0.0000</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment 4</td>
<td>-1.4483</td>
<td>0.1651</td>
<td>-1.7718 - -1.1247</td>
<td>-8.77</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>visiting 5</td>
<td>-0.7130</td>
<td>0.1599</td>
<td>-1.0265 - -0.3996</td>
<td>-4.46</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>visiting 6</td>
<td>-0.4788</td>
<td>0.1577</td>
<td>-0.7899 - -0.1698</td>
<td>-3.04</td>
<td>0.0024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>visiting 8</td>
<td>-0.2768</td>
<td>0.1479</td>
<td>-0.5667 - 0.0131</td>
<td>-1.87</td>
<td>0.0613</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment*VISIT 0 4</td>
<td>0.1009</td>
<td>0.2589</td>
<td>-0.4066 - 0.6083</td>
<td>0.39</td>
<td>0.6969</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment*VISIT 0 5</td>
<td>-0.3015</td>
<td>0.2654</td>
<td>-0.8216 - 0.2186</td>
<td>-1.14</td>
<td>0.2559</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment*VISIT 0 6</td>
<td>0.0369</td>
<td>0.2655</td>
<td>-0.4835 - 0.5573</td>
<td>0.14</td>
<td>0.8896</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment*VISIT 0 7</td>
<td>0.0294</td>
<td>0.2322</td>
<td>-0.7150 - 0.1952</td>
<td>-1.12</td>
<td>0.2630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment*VISIT 0 8</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000 - 0.0000</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Contrast Estimate Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Alpha</th>
<th>Confidence Limits</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogOR12</td>
<td>0.6780</td>
<td>0.1542</td>
<td>0.05</td>
<td>0.3759 - 0.9802</td>
<td>19.34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Exp (LogOR12)</td>
<td>1.9700</td>
<td>0.3037</td>
<td>0.05</td>
<td>1.4562 - 2.6649</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The output shows estimates and standard errors under the naive working correlation. The intercept
terms correspond to the intercept for the three cumulative logits defined on the response categories. The odds ratio of 1.97 in the ESTIMATE Statement Results indicates that the odds of Treatment B being in lower response categories is 1.97 times the odds of Treatment A being in lower response categories.

**MIXED-EFFECTS PROPORTIONAL ODDS MODEL**

Hedeker [2003] described a mixed-effects proportional odds model for ordinal data that accommodate multiple random effects. Proportional odds model is often referred as cumulative logit model. The effects of covariates in this model are assumed to be the same for each cumulative odds ratio. The cumulative probabilities for the C categories of the outcome Y as

$$P_{ij} = \Pr(Y_{ij} \leq c) = \sum_{k=1}^{C} p_{ijk}$$

where $p_{ijk}$ represents the probability of response in category k. The mixed-effects proportional odds model is specified in the form:

$$\log \left[ \frac{P_{ijk}}{1 - P_{ijk}} \right] = \gamma_k - Z_{ij} \quad (k=1,...,k),$$

Where $Z_{ij}=[\beta_0 + \beta_1 \times \text{Treatment}_i + \beta_2 \times \sqrt{\text{Visit}_j} + \beta_3 \times \text{Treatment}_i \times \sqrt{\text{Visit}_j} + \mu_{ij}]$

where Treatment is coded 0 for treatment A and 1 for treatment B. The random subject effects $\mu_{ij}$ are assumed to be normally distributed in the population of subjects with 0 mean and variance $\sigma^2$. $\gamma_k$ is model thresholds with k-1 increasing order. The marginal response probabilities in the k categories can be expressed with thresholds parameters and model intercepts. 0- $Z_{ij}$ represents the response lst logit (category 1 vs 2-4) at visit j, $\gamma_2 - Z_{ij}$ the 2nd logit (1-2 vs 3-4) at visit j, $\gamma_3 - Z_{ij}$ the 3rd logit (1-3 vs 4) at visit j. Parameter $\beta_1 + \beta_3 \sqrt{\text{Visit}_j}$ represents the visit-wise treatment differences relative to treatment A group, $\beta_2$ represents the square root of visit logit change for treatment A patients. The effects of the regression coefficients are conditional on the level of the random effect $\mu_{ij}$. Newton-Raphson or Quasi-Newton procedures to maximize the likelihood and adaptive Gaussian quadrature can be used to integrate out the random effects. It delivers exact ML estimates of the parameters if the number of quadrature points is large enough.

The subject-specific cumulative distribution function for each response category is defined as

$$\Pr(Y_{ij} = 1) = \frac{1}{1 + \exp(-0 - Z_{ij})},$$
$$\Pr(Y_{ij} = 2) = \frac{1}{1 + \exp(-\gamma_2 - Z_{ij})} - \Pr(Y_{ij} = 1)$$
$$\Pr(Y_{ij} = 3) = \frac{1}{1 + \exp(-\gamma_3 - Z_{ij})} - \Pr(Y_{ij} = 2)$$
$$\Pr(Y_{ij} = 4) = 1 - 1/\{1 + \exp(-\gamma_4 - Z_{ij})\}$$

The marginal probabilities are obtained by integrating over the random-effect distribution using numerical quadrature.

**SAS NLMIXED PROCEDURE**

The NLMIXED procedure provides exact maximum likelihood (ML) estimates. Unlike the GENMOD procedure, it allows for the explicit modeling of random effects. The following SAS code fits the described model by adaptive Gaussian quadrature:

```sas
ods output ParameterEstimates=esparam AdditionalEstimates=adparam;
PROC NLMIXED data=WKLY1 qpoints=100;
PARMS B0=0 B1=0 B2=0 B3=0 SD=1 THRESH1=1 THRESH2=1;
Z = B0 + B1*TREATMENT + B2*WEEKSQ + B3*TREATMENT*WEEKSQ + U;
IF (HAMDO1=1) THEN P = 1 / (1 + exp(-(0-Z)));
ELSE IF (HAMDO1=2) THEN P = (1/(1 + exp(-(THRESH1-Z)))) - (1/(1 + exp(-(0-Z))));
ELSE IF (HAMDO1=3) THEN P = (1/(1 + exp(-(THRESH1+THRESH2-Z)))) - (1/(1 + exp(-(0-Z))));
ELSE IF (HAMDO1=4) THEN P = 1 - (1/(1 + exp(-(THRESH1+THRESH2-Z))));
LL = LOG(P);
MODEL HAMDO1 ~ GENERAL(LL);
RANDOM U ~ NORMAL(0,SD*SD) SUBJECT=PATIENT;
```
ESTIMATE 'Threshold2' THRES1;
ESTIMATE 'Threshold3' THRES1 + THRES2;
RUN;

The PARMS statement lists names of parameters and specifies initial values. Provision of precise initial parameter estimates promotes convergence. Parameters not listed in PARMS statement are assigned an initial value of 1. General (l) in the MODEL statement specifies a general log likelihood function that you construct using SAS programming statements. The only distribution currently available for the random effects is normal (m,v) with mean m an variance v. The subject= patient determines when new realizations of the random effects are assumed to occur. The input data set should be clustered according to this variable. QPOINTS specifies the number of quadrature points to be used during the evaluation of integrals. You can increase the number of quadrature points to get a better approximation, but the fitting procedure takes longer.

SELECTED SAS OUTPUT

The maximum likelihood estimates are $\hat{\beta}_1 = -0.5605$ (SE=0.7787), $\hat{\beta}_2 = -1.7388$ (SE=0.2446), and $\hat{\beta}_3 = -0.1810$ (SE=0.3043). The results indicate that the treatment groups do not significantly differ at baseline, the Treatment A group does improve over time, and that the Treatment B group has greater improvement over time, relative to the Treatment A group.

SUBJECT-SPECIFIC ESTIMATED PROBABILITIES PLOTS

Scatter Plot of Estimated Probabilities at last visit for Treatment A patients
Scatter Plot of Estimated Probabilities at last visit for Treatment B patients
The above figures depict the estimated probability of being normal at the end of study for each patient.

MARGINAL ESTIMATED PROBABILITY PLOTS
The following figures display the marginal estimated probability for each ordinal response across time by treatment.

CONCLUSION
This paper describes the framework of the mixed-effects proportional odds model besides CMH and GEE methods. The analysis of the Hamilton Depression dataset demonstrates how to estimate subject-specific influence and population averaged trend. Since the NLMIXED procedure requires more computation work, a SAS macro is also devised to automate fitting models. The macro allows you to write simpler
syntax. The syntax for the analysis is the following:

data orddb;
  set efficacy;
  if visit = 1 then week = -2;
  if visit = 2 then week = -1;
  if visit = 3 then week = 0;
  if visit = 4 then week = 1;
  if visit = 5 then week = 2;
  if visit = 6 then week = 3;
  if visit = 7 then week = 4;
  if visit = 8 then week = 6;
  if visit = 9 then week = 8;
weeksq=sqrt(week);
where 4<=visit<=9 and THERCODE in ('1','2');
run;
ods output ParameterEstimates=esparam AdditionalEstimates=adparam;
PROC NLMIXED data=WKLY1 qpoints=100;
PARMS B0=0 B1=0 B2=0 B3=0 SD=1 THRES1=1 THRES2=1;
Z = B0 + B1*TREATMENT + B2*WEEKSQ + B3* TREATMENT * WEEKSQ + U;
IF (HAMD01=1) THEN P = 1 / (1 + EXP(-(0-Z)));
ELSE IF (HAMD01=2) THEN P = (1/(1 + EXP(-(THRES1-Z)))) - (1/(1 + EXP(-(-0-Z))));
ELSE IF (HAMD01=3) THEN P = (1/(1 + EXP(-(THRES1+THRES2-Z)))) - (1/(1 + EXP(-(-THRES1-Z))));
ELSE IF (HAMD01=4) THEN P = 1 - (1 / (1 + EXP(-(-THRES1+THRES2-Z))));
LL = LOG(P);
MODEL HAMD01 ~ GENERAL(LL);
RANDOM U ~ NORMAL(0,SD*SD) SUBJECT=PATIENT;
ESTIMATE 'Threshold2' THRES1;
ESTIMATE 'Threshold3' THRES1 + THRES2;
RUN;
PROC IML;
x0 = { 1 0 1.00000 0,
        1 0 1.41421 0,
        1 0 1.73205 0,
        1 0 2.00000 0,
        1 0 2.44949 0,
        1 0 2.82843 0};
x1 = { 1 1 1.00000 1.00000,
        1 1 1.41421 1.41421,
        1 1 1.73205 1.73205,
        1 1 2.00000 2.00000,
        1 1 2.44949 2.44949,
        1 1 2.82843 2.82843};
sdu = {2.114};
beta = {5.2656, -0.5605, -1.7388, -0.1810};
threshold = {2.1734, 4.5048};
pi = 3.141592654;
nt = 6;
ivector = J(nt,1,1);
zvector = J(nt,1,1);
evector = (15/16)**2 * (pi**2)/3 + ivector;
ematrix= diag(evector);

vary = zvector * sdu*sdu * T(zvector) + ematrix;
sdy = sqrt(vecdiag(vary) / vecdiag(ematrix));
ord00 = (0 - x0*beta) / sdy;
ord01 = (threshold(1) - x0*beta) / sdy;
ord02 = (threshold(2) - x0*beta) / sdy;
ord10 = (0 - x1*beta) / sdy;
ord11 = (threshold(1) - x1*beta) / sdy;
ord12 = (threshold(2) - x1*beta) / sdy;
trt0a = 1 / (1 + EXP(0 - ord00));
trt0b = 1 / (1 + EXP(0 - ord02));
trt0c = 1 / (1 + EXP(0 - ord03));
trt1a = 1 / (1 + EXP(0 - ord11));
trt1b = 1 / (1 + EXP(0 - ord12));
trt1c = 1 / (1 + EXP(0 - ord13));
print "MIXED-EFFECTS PROPORTIONAL ODDS MODEL";
print "Approximate Marginalization Probability ";
print "marginal prob for Treatment A - catg 1 " trt0a [FORMAT=8.4];
print "marginal prob for Treatment A - catg 2 " (trt0b-trt0a) [FORMAT=8.4];
print "marginal prob for Treatment A - catg 3 " (trt0c-trt0b) [FORMAT=8.4];
print "marginal prob for Treatment A - catg 4 " (1-trt0c) [FORMAT=8.4];
print "marginal prob for Treatment B - catg 1 " trt1a [FORMAT=8.4];
print "marginal prob for Treatment B - catg 2 " (trt1b-trt1a) [FORMAT=8.4];
print "marginal prob for Treatment B - catg 3 " (trt1c-trt1b) [FORMAT=8.4];
print "marginal prob for Treatment B - catg 4 " (1-trt1c) [FORMAT=8.4];
run;
quit;

Sample Syntax for the devised macro:

%rmordinal (indb= ORDDB,      /**input dataset**/  
y= HAMD01,        /**response variable**/  
visitV= WEEKSQ,   /**Visit variable**/   
visitL= 6,       /**Visit Level**/   
interV= B0,       /* Intercept Variable */   
randV= U,             /* Random Variable */   
trt= TREATMENT,       /* Treatment Variable- 2 level only */   
model= B0 + B1*TREATMENT + B2*WEEKSQ + B3* TREATMENT * WEEKSQ + U,   
/**model specification for proc NLMIXED **/   
DisTV= GENERAL(LL), /** Specifies the conditional distribution of  
the data given the random effects **/   
);

STATISTICAL CONCEPT OF UNDERSTANDING THE EXPERIMENT. REFERENCES
22:1433–1446
Kenward, M.G., and Molenberghs, G. (1998) Likelihood based frequentist inference when data are 
missing at random.
logistic regression model for binary longitudinal outcomes.  Biometrics and Reporting.
Ashby,M., Neuhaus, J., Hauck W., Baccchetti, P., Heilbrow, D., Jewell, N., Segal,M. and Fusaro,R. 
Medicine 11.

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