

A Step-by-Step Programming Approach to Summarize Best Response in Patients with Multiple Myeloma Who Had Positive and Negative MRD Test Results

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Stream: Therapeutic Areas Specific Topics (TA)

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1. Background

- MRD Test
- Multiple Myeloma (MM)
- IMWG Response Criteria for Multiple Myeloma

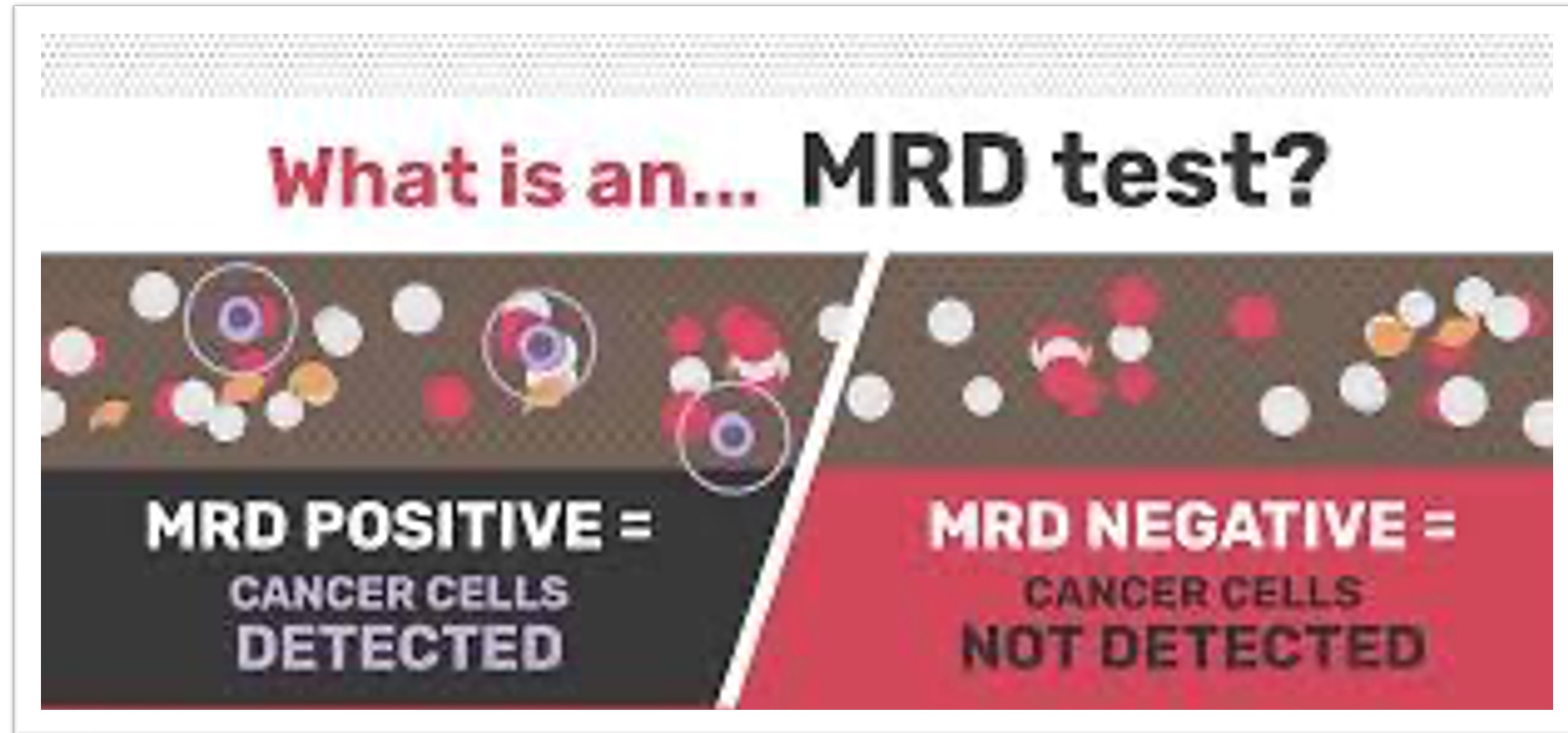
2. Understanding Data Structure and Programming Logic

- Investigator Assessed Response
- Identifying Best Response by MRD Test Results
- Hypothetical Data Structure
- Programming Steps Involved in Merging data
- Programming Steps Involved in Output Generation

3. Conclusion

4. Q&A ?

Minimal Residual Disease (MRD) Test



Widely Used

**Highly sensitive
testing method**

**Effect of ongoing
treatment can be seen**

Multiple Myeloma (MM)

- Multiple Myeloma (MM) is a type of blood cancer that develops in plasma cells inside the bone marrow.
- In healthy bone marrow, normal plasma cells make antibodies to protect the body from infection.
- Plasma cells are transformed into cancerous cells that grow out of control and reduce normal blood cells (RBCs, WBCs, and Platelets) that help fight infection.
- These malignant plasma cells then produce an abnormal antibody called M protein.
- Detection of M protein confirms presence of MM.

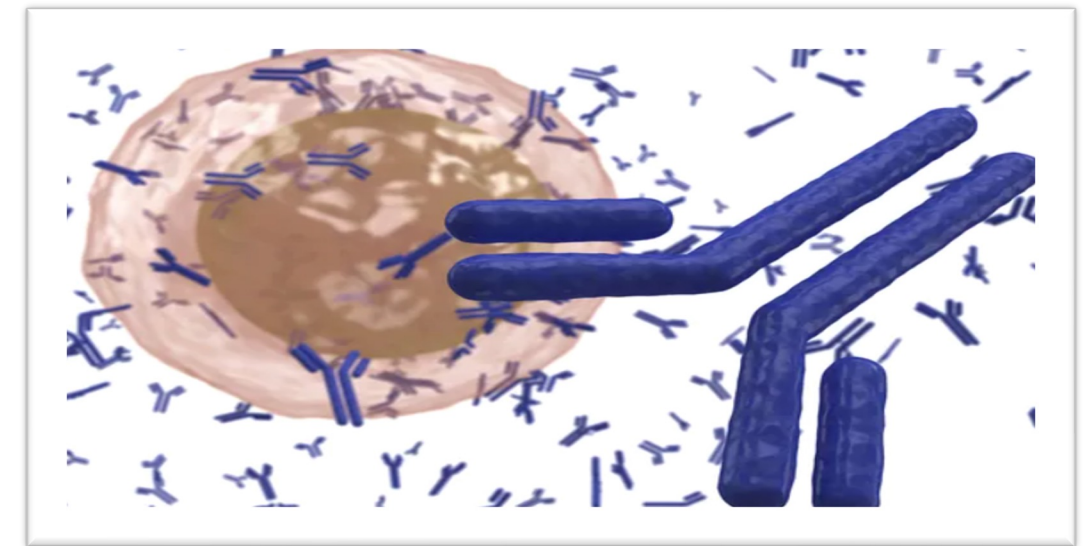


Figure - Plasma cell producing M-protein antibody

The International Myeloma Working Group (IMWG) provided guidance on response evaluation criteria (2011) which diagnoses Multiple myeloma:

Table 1

Definition of response according to the last classification of the IMF.

Categories of response according to IMF 2011	Level of detection
PR	MC < 50%
VGPR	MC < 90%
nCR	MC 0.1–0.5 g/dl (EF–/IF+)
CR	MC ≤ 0,5 g/dl (IF–) PC in BM < 5%
Stringent CR	sFLC ratio +BM ICH
Immunophenotypic CR	sCR+ nonaberrant PC in 1,000,000 cells
Molecular CR	CR+ nonclonal plasma cells with sensitivity > 10 ⁻⁵

In 2014, IMWG updated the diagnostic criteria for MM to add three specific biomarkers that can be used to diagnose the disease in patients who did not have CRAB features [CRAB: C = Calcium elevation; R = Renal insufficiency; A = Anemia; B = Bone abnormalities; nCR = near complete response].

Investigator Response

- Investigator responses and MRD test results are collected on CRF .
- A summary report is created as per below shown mock-table which shows relationship between response and MRD test results.

	Table 2		
Summary of Best Response by MRD Test Results			
Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	XX	XX	XX
VGPR	XX	XX	XX
PR	XX	XX	XX
MR	XX	XX	XX
SD	XX	XX	XX
PD	XX	XX	XX
Missing	XX	XX	XX

Note: CR – Complete Response, sCR – Stringent Complete Response, VGPR – Very Good Partial Response, PR – Partial Response, MR – Minimal Response, SD – Stable Disease and PD – Progressive Disease

Identifying Best Response by MRD Test Results

Table 3			
Summary of Best Response by MRD Test Results			
All Lines			
Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
VGPR	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
PR	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
MR	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
SD	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
PD	XX	XX	XX
1 st Line Response	XX	XX	XX
2 nd Line Response	XX	XX	XX
3 rd Line Response	XX	XX	XX
Missing	XX	XX	XX

Note: CR – Complete Response, sCR – Stringent Complete Response, VGPR – Very Good Partial Response, PR – Partial Response, MR – Minimal Response, SD – Stable Disease and PD – Progressive Disease

Hypothetical Data Structure

Let's look at some examples of source data that will be used to understand programming logic and how reports are developed.

USUBJID	LINE	PHASE	SEQNUM	DRUG	TSTART	TEND
1001	1	Induction	1	ABC	12-Jun-10	08-Dec-11
1001	1	SCT	2	A	20-Dec-11	20-Dec-11
1001	1	Maintenance	3	Z	23-Apr-12	13-Feb-17
1001	2	Induction	4	CDE	23-Feb-17	12-Sep-17
1001	2	Consolidation	5	X	20-Sep-17	11-Nov-17
1001	2	Maintenance	6	Y	21-Dec-17	06-Feb-18
1001	3	Induction	7	Z	16-Feb-18	26-Jun-18
1002	1	Induction	1	ABC	12-Jun-10	08-Dec-11
1002	1	Consolidation	2	C	20-Dec-11	20-Dec-11
1002	2	Maintenance	3	BCD	23-Apr-12	13-Feb-17
1003	1	Induction	1	DEF	23-Feb-17	12-Sep-17
1003	1	SCT	2	D	20-Sep-17	11-Nov-17
1003	1	Maintenance	3	X	21-Dec-17	05-Feb-18
1003	2	Consolidation	4	XY	06-Feb-18	26-Jun-18
1003	2	Maintenance	5	XYZ	16-Aug-18	30-Sep-18



USUBJID	LINE	LSTART	LEND
1001	1	12-Jun-10	13-Feb-17
1001	2	23-Feb-17	06-Feb-18
1001	3	16-Feb-18	26-Jun-18
1002	1	12-Jun-10	20-Dec-11
1002	2	23-Apr-12	13-Feb-17
1003	1	23-Feb-17	05-Feb-18
1003	2	06-Feb-18	30-Sep-18

Table 4aa: Transformed data

Source Data # 1 - Table 4a: Multiple Lines of Treatment

Annotation:

- USUBJID = Unique subject identifier
- LINE = Multiple lines of treatment received by a patient
- PHASE = Various phases of treatment
- SEQNUM = Treatment sequence number (also known as regimen number)
- DRUG = Treatment sequence
- TSTART = Treatment start date
- TEND = Treatment end date

```
proc sql noprint;
  create table t4aa as select subjid, line, min(tstart) as lstart format date9.,
                             max(tend) as lend format date9.
  from t4a
  group by subjid, line;
quit;
```

Hypothetical Data Structure ...cont.

USUBJID	MRDDT	MRDRSPN	MRDRSP
1001	12-Nov-10	1	MRD +ve
1001	13-Jan-11	2	MRD -ve
1001	23-Feb-11	1	MRD +ve
1001	27-Apr-11	3	MRD +ve
1001	25-May-11	1	MRD +ve
1002	23-Feb-17	1	MRD -ve
1002	17-Mar-17	2	MRD -ve
1002	19-Apr-17	3	MRD +ve
1002	21-May-17	1	MRD +ve
'1002	16-June-17	1	MRD +ve
1003	23-Feb-18	1	MRD +ve
1003	17-Mar-18	3	MRD -ve
1003	19-Apr-18	2	MRD -ve
1003	21-May-18	1	MRD +ve
1003	05-Sep-18	2	MRD -ve

Source Data # 2 - Table 4b: MRD Test Results Data as per CRF

Hypothetical Data Structure ...cont.

USUBJID	ASSESSYN	ASSDT	MMRESPN	MMRESP
1001	Yes	23-Feb-11	1	Complete Response (CR)
1001	Yes	13-Mar-11	6	Progressive Disease (PD)
1001	Yes	14-Jun-11	3	Partial Response (PR)
1001	Yes	23-Apr-17	2	Very Good Partial Response (VGPR)
1001	Yes	23-Jul-17	5	Stable Disease (SD)
1001	Yes	23-Aug-17	3	Partial Response (PR)
1001	Yes	25-Jun-18	7	Missing
1002	Yes	23-Feb-10	3	Partial Response (PR)
1002	Yes	06-Mar-10	6	Progressive Disease (PD)
1002	Yes	16-Jun-10	2	Very Good Partial Response (VGPR)
1002	Yes	11-Jul-11	6	Progressive Disease (PD)
1003	Yes	06-Aug-17	5	Stable Disease (SD)
1003	Yes	06-Sep-17	4	Minimal Response (MR)
1003	Yes	14-Aug-18	6	Progressive Disease (PD)
1003	Yes	06-Sep-18	7	Missing
1003	Yes	27-Sep-18	3	Partial Response (PR)

Source Data # 3 - Table 4c: Response Evaluation Data as per CRF

Programming steps involved in Merging data

Final Data: In the current scenario, we create the cartesian product by merging all three data using PROC SQL.

```
proc sql;  
  create table t4abc as select a.*, b.mrddt, b.mrdrspn, b.mrdrsp, c.assdt, c.mmrespn, c.mmresp  
  from t4aa a left join t4b b  
  on a.subjid=b.subjid and a.lstart<=c.mrddt<=c.lend  
  left join t4c c  
  on a.subjid=c.subjid and a.lstart<=b.assdt<=c.lend  
  order by a.subjid, a.line;  
quit;
```



```
** Check to make sure no duplicates after merging all data **;  
proc sort data=t4abc out=s_t4abc nodupkey;  
  by subjid line mrdrspn mrdrsp mrddt assdt ;  
run;
```

Challenges

- Multiple observations per subject is a challenge. Hence, PROC SQL is more appropriate in this situation.
- Number of events of interest

Code to produce Table 2

```
** Step 1(a). Identify Best response per subject from multiple responses **;  
proc sql;  
  create table bestresp as  
  select subjid, mdrdspn, mdrdsp, min(mmrespn) as bestresp  
  from s_t4abc  
  group by subjid, mdrdspn, mdrdsp, mmrespn, mmresp;  
quit;  
  
** Step 1(b). Get counts of Best response by MRD overall tests **;  
proc sql;  
  create table mrd_all as  
  select mdrdspn, mdrdsp, count(subjid) as bresp_mrd_all  
  from bestresp  
  group by mdrdspn, mdrdsp, bestresp;  
quit;  
  
** Step 1(c). Get counts of Best response by MRD +ve tests **;  
proc sql;  
  create table mrd_pos as  
  select mdrdspn, mdrdsp, count(subjid) as bresp_mrd_pos  
  from bestresp  
  where mdrdsp = 'MRD +ve'  
  group by mdrdspn, mdrdsp, bestresp;  
quit;  
  
** Step 1(d). Get counts of Best response by MRD -ve tests **;  
proc sql;  
  create table mrd_neg as  
  select mdrdspn, mdrdsp, count(subjid) as bresp_mrd_neg  
  from bestresp  
  where mdrdsp = 'MRD -ve'  
  group by mdrdspn, mdrdsp, bestresp;  
quit;  
  
** Step 1(e). Merge all to get final data for Table 2 **;  
data tab2;  
  merge mrd_all mrd_pos mrd_neg;  
  by mdrdspn mdrdsp bestresp;  
run;
```

	Table 2		
Summary of Best Response by MRD Test Results			
Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	1	0	1
VGPR	2	0	2
PR	4	1	3
MR	1	0	1
SD	2	1	2
PD	4	0	4
Missing	2	1	1

Code to produce Table 3

- Tweak to programming steps 1(b) through 1(e) are needed like step 2(a).
- The rest of the code is the same as used for Table 2 (1(b) - 1(e)).
- Best response is counted per subject, per MRD result, and per line of treatment.

```
** Step 2(a). Identify Best response per subject per treatment line from multiple responses **;  
proc sql;  
  create table bestresp as  
  select subjid, mrdrspn, mrdrsp, line, min(mmrespn) as bestresp  
  from s_t4abc  
  group by subjid, mrdrspn, mrdrsp, line, mmrespn, mmresp;  
quit;
```

Table 3			
Summary of Best Response by MRD Test Results			
All Lines			
Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	1	0	1
1 st Line Response	1	0	1
2 nd Line Response	0	0	0
3 rd Line Response	0	0	0
VGPR	2	0	2
1 st Line Response	0	0	0
2 nd Line Response	2	0	2
3 rd Line Response	0	0	0
PR	4	1	3
1 st Line Response	0	1	1
2 nd Line Response	0	0	1
3 rd Line Response	0	0	0
MR	1	0	1
1 st Line Response	1	0	1
2 nd Line Response	0	0	0
3 rd Line Response	0	0	0
SD	2	1	2
1 st Line Response	1	1	1
2 nd Line Response	1	0	1
3 rd Line Response	0	0	0
PD	4	0	4
1 st Line Response	2	0	2
2 nd Line Response	2	0	2
3 rd Line Response	xx	0	0
Missing	2	1	1

Conclusion

MRD testing
widely used &
accepted

**MRD test results &
best response**
show efficacy

Multiple Myeloma
blood cancer of
bone marrow

M-Protein antibody
are used for
MM Diagnosis

Future guidance
on statistical
programming



THANK YOU