Heart Diagnostics

DRAFT

A Rule Modeling Case Study Using Corticon Business Rule Studio

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The Business Use Case

Every cell in the body produces cholesterol. Additional cholesterol, received through the diet, is absorbed by the small intestine. Both synthesized and absorbed cholesterol play a role in atherosclerosis development as it all, sooner or later, ends up in LDL.

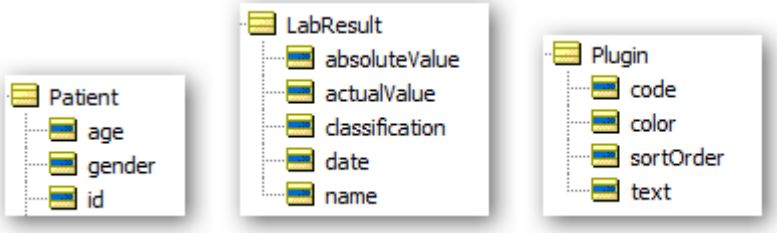
Blocking cholesterol synthesis with a statin lowers LDL cholesterol as does blocking cholesterol absorption with an inhibitor like Ezetimibe (otherwise it's repetitive). Every person is different when it comes to cholesterol balance. Some people synthesize cholesterol more than they absorb, while others absorb more than they synthesize. Knowing whether a patient is a hyper synthesizer or a hyper absorber allows for better treatment as response to drug therapy varies accordingly. A synthesizer responds well to a statin while a hyper absorber may benefit more from combination therapy with Ezetimibe. Knowing what therapy works best in advance will allow for a more successful and cost effective treatment strategy.

Lathosterol, the direct precursor of cholesterol, can be measured in plasma or serum. Eighty percent of synthesized cholesterol goes through lathosterol, while only 20% goes through desmosterol. Therefore lathosterol is the only valid marker of cholesterol production. People who overproduce cholesterol have elevated levels of lathosterol normalized to total blood cholesterol levels. Markedly elevated levels of lathosterol identify patients with increased risk of premature coronary heart disease.

This decision service analyzes lab results to determine risk and lifestyle and therapy options

Building the Data Model

We first identify the business objects required for this model:



And the relationship between them:
Patients will have zero or more lab results and after the rules have executed there will be zero or more plugins (objects that contain the conclusions and recommendations made by the rules)

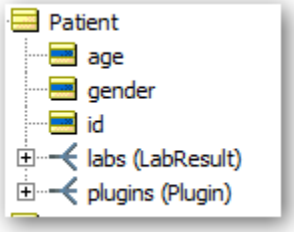


Figure 1 Vocabulary

Modeling the Rules

R1-R9 The Main Rules

Let's take a look at the main rules that look at cholesterol production and absorption classifications.
Each of these can be classified as Optimal, Borderline or High.
This means there are 3x3=9 possible combinations to deal with.
The Appendix lists each of the nine rules.
Here are two of them:

1) **Borderline Production, Borderline Absorption**
   - BORDERLINE cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and statin therapy if LDL-C lowering is indicated.

2) **High Production, Borderline Absorption**
   - HIGH cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and statin therapy if LDL-C lowering is indicated.

The first step in modeling these rules is to copy/paste the rules into the rule statement section of the rule sheet:

Rule Statements

...	Text
0	Production classification is based on {production.name}({production.classification})
1	- BORDERLINE cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification and statin therapy if LDL-C lowering is indicated.
2	- HIGH cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification and statin therapy if LDL-C lowering is indicated.
3	- HIGH cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification, statin and ezetimibe therapy if LDL-C lowering is indicated.
4	- HIGH cholesterol production and OPTIMAL absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification and statin therapy if LDL-C lowering is indicated.
5	- BORDERLINE cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification, statin and ezetimibe therapy if LDL-C lowering is indicated.
6	- OPTIMAL cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification and ezetimibe therapy if LDL-C lowering is indicated.
7	- OPTIMAL cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk. - Lifestyle modification and ezetimibe therapy if LDL-C lowering is indicated.
8	- OPTIMAL cholesterol production and OPTIMAL absorption. -(no treatment considerations)
9	-BORDERLINE cholesterol production and OPTIMAL absorption may be associated with elevated LDL-C levels and increased heart disease risk. -Lifestyle modification and statin therapy if LDL-C lowering is indicated.

Then each combination of value can be mapped out in the rule columns

Conditions	0	1	2	3	4	5	6	7	8	9
production.classification		'Borderline'	'High'	'High'	'High'	'Borderline'	'Optimal'	'Optimal'	'Optimal'	'Borderline'
absorption.classification		'Borderline'	'Borderline'	'High'	'Optimal'	'High'	'Borderline'	'High'	'Optimal'	'Optimal'

Then we add the appropriate action for each of the nine cases.
Here are the first few rules

	Conditions	0	1	2	3
a	production.classification		'Borderline'	'High'	'High'
b	absorption.classification		'Borderline'	'Borderline'	'High'
	Actions				
	Post Message(s)	✉	✉	✉	✉
A	plugin += Plugin.new[text=production.classification + ' cholesterol production and ' + absorption.classification + ' absorption may be associated with elevated LDL-C levels and increased heart disease risk.']	☐	☑	☑	☑
B	plugin += Plugin.new[text='Lifestyle modification and statin therapy if LDL-C lowering is indicated.']	☐	☑	☑	☐
C	plugin += Plugin.new[text='Lifestyle modification and statin and '+ cellValue + ' therapy if LDL-C lowering is indicated.']				'ezetimibe'
D	plugin += Plugin.new[text='Cholesterol levels are optimal - no intervention needed']	☐	☐	☐	☐

Figure 2 The Core Rule Sheet

The actions of the rules are to create the text values that will be in the plugin objects that eventually appear on the report.

The syntax is basically **plugin += Plugin.new[text='xxxxx']**

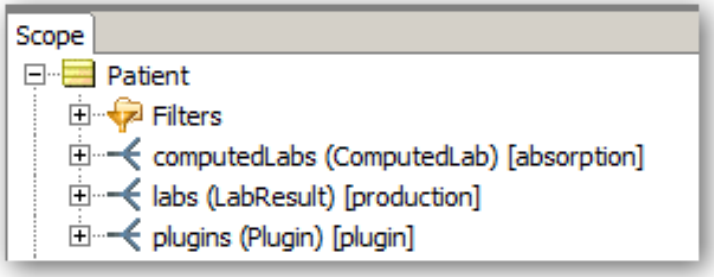
Which means create a new plugin object with a text value of 'xxxxx' and add it to the list of plugins for this patient.

In the case of rules 1 and 2 the text is fixed. But in rule 3 you can see how a variable text value (Ezetimibe) can be embedded in the text by using the keyword **cellValue**.

The Concept of Scope

Because the data model contains relationships between the Patient object and the LabResults and Plugins we need to tell the rule sheet what part(s) of the hierarchy we will be using. This is important because it enables Corticon to make sure that when it analyzes lab results it's using the ones that belong to the correct patient.

Here's the scope section:

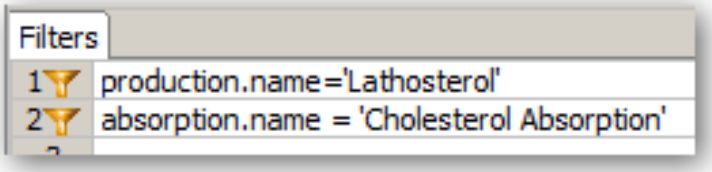


Notice the names in square brackets [ ]. These are aliases to the objects that we use in the rules.

So the reference to production.classification means the classification of the lab result passed in.

But how do we know which of the many lab results this actually refers to?

That's where the filter section comes into play:



The filters tell us that the production classification that's being tested is called Lathosterol and the absorption classification is called "Cholesterol Absorption"
But that's not one of the lab results that is passed in to the rules.
What does get passed in are the classifications for Beta-Sitosterol and Campesterol and the documented rules tell us that we need to take the higher of these two classifications.
That leads us to a subordinate rule sheet whose purpose is to compare Beta-Sitosterol and Campesterol and determine the higher classification.
Here's the first few rules of that sheet:

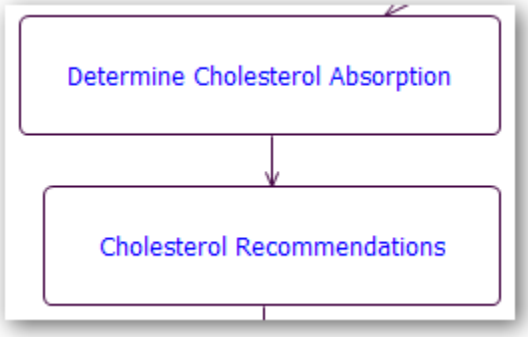
	Conditions	1	2	3
a	betaSitosterol.classification	'Optimal'	'Optimal'	'Optimal'
b	campesterol.classification	'Optimal'	'Borderline'	'High'
c				
d				
	Actions			
	Post Message(s)			
A	cholesterolAbsorption+=ComputedLab .new[name='Cholesterol Absorption',classification=cellValue]	'Optimal'	'Borderline'	'High'
	Overrides			

Rule Statements

Text
Cholesterol Absorption classification is based on the higher of Campesterol ({campesterol.classification}) and Beta-Sitosterol ({betaSitosterol.classification})
With regard to absorption use only normalized beta-sitosterol and normalized campesterol, even if there an alert value very high cholestanol, for normalized beta-sitosterol and campesterol, the higher value supercedes the lower value:

Figure 3 Rules for Absorption Classification

Notice that the action of these rules is to create that missing "Cholesterol Absorption" lab result as an instance of a new business object called ComputedLab. That's what gets referred to in the previous rule sheet for absorption classification.
These two sheets will then work in conjunction. To show this we put them in the rule flow diagram:



At this point we have the main rules for this decision.
But there are a lot of special cases and exceptions described in the documentation.
From a business rules perspective these are not special cases or exceptions – they are simply more business rules that are required for a complete solution.

Let's work through some of these.

R10-R15 Very High Values

Rules 10-15 deal with Very High levels of lipids. E.g.

10) Very High Lathosterol (Action Value)
Lathosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol production.

11) Very High Desmosterol (Action Value)
Desmosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol production..

12) Very High Beta-Sitosterol and Campesterol (Action Value)
Beta-sitosterol level is very HIGH at [_] mg/L. Campesterol level is very HIGH at [_] mg/L. Very high absolute cholesterol absorption values may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia and increased heart disease risk.

13) Very High Beta-sitosterol (Action Value)*
Beta-sitosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia, and increased heart disease risk.

14) Very High Campesterol (Action Value)*
Campesterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia, and increased heart disease risk.

15) Very High Cholestanol (Action Value)
Cholestanol level is very HIGH at [__]mg/L, and may be associated with tendon xanthomas, neurological disease, and cerebrotendinous xanthomatosis.

One way to model this (there are always alternatives) is:

Conditions	0	1	2	3	4	5	6
lab.name		'Lathosterol'	'Desmosterol'	'Beta-Sitosterol'	'Campesterol'	'Cholestanol'	-
lab.absoluteValue		> 7.0	> 5.0	> 7.0	> 10.0	> 8.0	-
betaSitosterol.actionValue		-	-	-	-	-	'Very High'
campesterol.actionValue		-	-	-	-	-	'Very High'
Actions							
Post Message(s)							
lab.actionValue		'Very High'	'Very High'	'Very High'	'Very High'	'Very High'	
Overrides							

ule Messages | Natural Language | History | Properties | Rule Statements

Post	Alias	Text
Warning	lab	R10: Lathosterol: Very High > 7.0 mg/L *Action Value ({lab.absoluteValue}) consistent with markedly increased cholesterol production.
Warning	lab	R11: Desmosterol: Very High > 5.0 mg/L *Action Value ({lab.absoluteValue}) consistent with markedly increased cholesterol production.
Warning	lab	R13: Beta-Sitosterol: Very high: > 7.0 mg/L * Action Value ({lab.absoluteValue}) consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, ...
Warning	lab	R14: Campestrol: Very high: > 10.0 mg/L * Action Value ({lab.absoluteValue}) consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia, and increased heart disease risk.
Warning	lab	R15: Cholestanol: Very high: > 8.0 mg/L * Action Value ({lab.absoluteValue}) and may be associated with tendon xanthomas, neurological disease, and cerebrotendinous xanthomatosis.
Warning	Patient	R12: Very High Beta-Sitosterol and Campesterol (Action Value) Beta-sitosterol level is very HIGH at [{betaSitosterol.absoluteValue}] mg/L. Campesterol level is very HIGH at [{campesterol.absoluteValue}] mg/L. Very high absolute cholesterol absorption values may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia and increased heart disease risk

Figure 4 Very High Value Rules

However it's possible that the calling application may already provide the AVH classification in the input data

R16-R19 Below Detection Limit

Rules 16-19 deal with values below the detection limit

16) Lathosterol below detection limit*
Lathosterol level is BELOW detection limit, indicating DECREASED cholesterol production.
17) Desmosterol below detection limit*
Desmosterol level is BELOW detection limit.
18) Beta-sitosterol below detection limit*
Beta-sitosterol level is BELOW detection limit, indicating DECREASED cholesterol absorption.
19) Campesterol below detection limit*
Campesterol level is BELOW detection limit, indicating DECREASED cholesterol absorption.

This can be modeled like this

	Conditions	0	1	2	3	4	5
a	lab.name		'Lathosterol'	'Desmosterol'	'Beta-Sitosterol'	'Campesterol'	'Cholestanol'
b	lab.classification		'BDL'	'BDL'	'BDL'	'BDL'	'BDL'
c							
d							
	Actions						
	Post Message(s)						
A							
B							
C							
	Overrides						

Rule Messages | Natural Language | History | Properties | Rule Statements

Ref	Post	A...	Text
1	Warning	lab	R16: Lathosterol level is BELOW detection limit, indicating DECREASED cholesterol production.
2	Warning	lab	R17: Desmosterol level is BELOW detection limit.
3	Warning		R18: Beta-sitosterol level is BELOW detection limit, indicating DECREASED cholesterol absorption
4	Warning	lab	R19: Campesterol level is BELOW detection limit, indicating DECREASED cholesterol absorption.
5	Violation	lab	no action defined for Cholestanol BDL

Figure 5 BDL Rules

D2 Missing Values

If any value is missing (usually desmosterol for older patient reports), XXXXXXXXXXX (currently not possible with Boolean structure – current Interpretation #22)

This can be modeled as

	Conditions	1	2
a	lab.classification	'Missing'	not {'BDL', 'TNP', 'AVH', 'AVL', 'CriticalLow', 'CritalHIgh', 'AlertHigh', 'AlertLow', 'Missing'}
	Actions		
	Post Message(s)		
A			
	Overrides		

Rule Messages | Natural Language | History | Properties | Rule Statements

Ref	Post	Alias	Text
1	Warning	lab	If any value is missing (usually desmosterol for older patient reports), XXXXXXXXXXX (currently not possible with Boolean structure – current Interpretation #22)
2	Violation	lab	Invalid value for lab classification ({lab.classification})
			Alternative: The individual sheets for the various labs could contain the specific rules for missing values - this would be a better design since you might want to do dofferent things when different values are missing. In this sheet we don't distinguish between the various labs

Figure 6 Missing Values Rules

D1 Variations in Lathosterol and Desmosterol Classifications

If desmosterol is at different category level (optimal, borderline or high) than lathosterol: insert statement: "Desmosterol accounts for 20% of production."

	Conditions	0	1	2
a	desmosterol.classification <> lathosterol.classification		T	
b				
c				
d				
	Actions			
	Post Message(s)			
A	plugin+=Plugin.new[text='Desmosterol accounts for 20% of production.']		☑	
	Overrides			

Rule Messages | Natural Language | History | Properties | Rule Statements

Ref	Post	Alias	Text
1	Info	desmosterol	If desmosterol is at different category level (optimal, borderline or high) than lathosterol: insert statement: "Desmosterol accounts for 20% of production."

Figure 7 Lathosterol/Campesterol Differences

Question: Does this only apply to optimal, borderline and high or to all classifications?

Assembling the Decision service

The rule flow is the mechanism for assembling a decision service from the various rule sheets: For example:

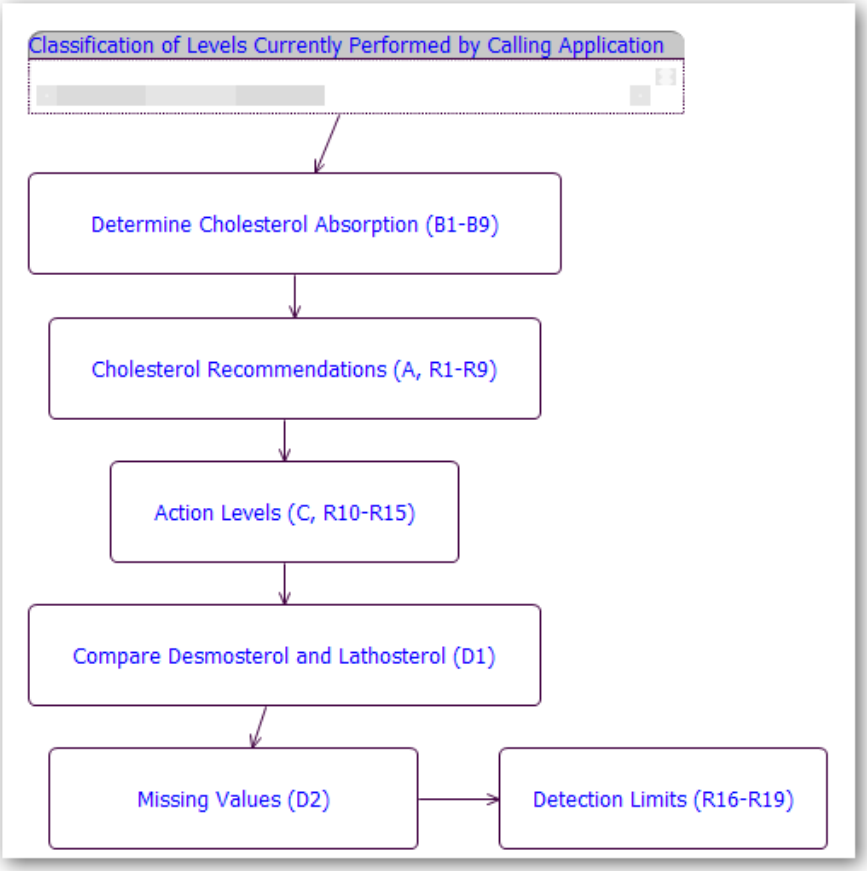


Figure 8 The Rule Flow

We can specify the properties of this rule flow as follows:

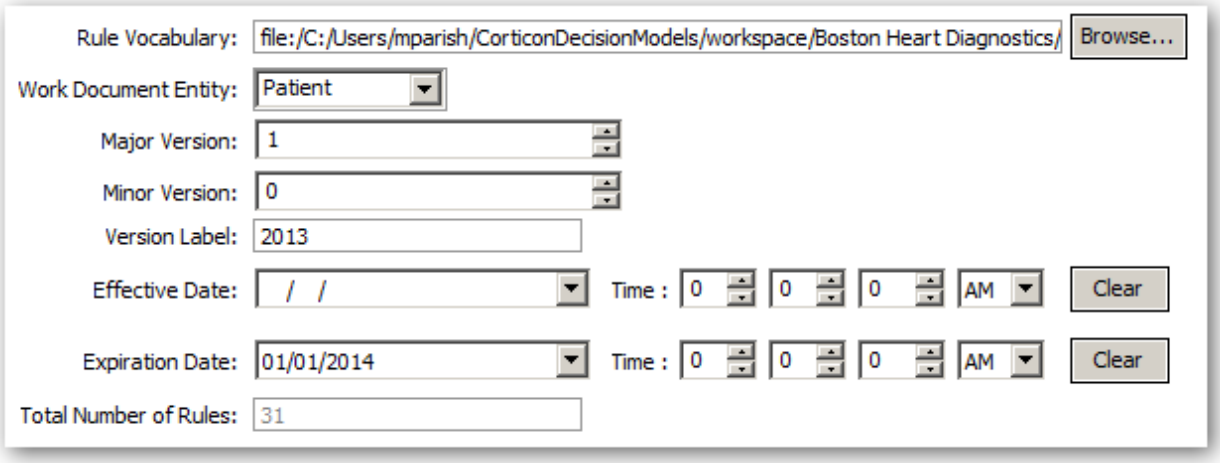


Figure 9 Rule Flow Properties

Alternative Structure

If we later decide to do the classification inside Corticon we would simply add rule sheets for each of the lipids:

Lathosterol could look like this:

	Conditions	0	1	2	3	4
a	lathosterol.absoluteValue*100/totalCholesterol.absoluteValue		< 90	90..160	> 160	-
b	lathosterol.absoluteValue		-	-	-	> 7
-						
	Actions					
	Post Message(s)					
A	lathosterol.classification		'Optimal'	'Borderline'	'High'	
B						
C						
D						
	Overrides					

Rule Messages | Natural Language | History | Properties | Rule Statements

Ref	Post	Alias	Text	Source Name	Source Link
1	Info	lathosterol	Lathosterol: Optimal: <90 µmol x 100/mmol of Total Cholesterol		
2	Warning	lathosterol	Lathosterol: Borderline: 90 -160 µmol x 100/mmol of Total Cholesterol		
3	Violation	lathosterol	Lathosterol: High > 160 µmol x 100/mmol of Total Cholesterol		
4	Warning	lathosterol	Lathosterol: Very High > 7.0 mg/L *Action Value ({lathosterol.absoluteValue})		
			Note for programming with regard to production: always use the normalized lathosterol to categorize people as optimal, borderline, or high, even if there is an alert value on desmosterol (reason: 80% of the production goes through lathosterol).	Cholesterol Balance coding.docx	Shalom Keynan
			Lathosterol, the direct precursor of cholesterol, can be measured in plasma or serum. Eighty percent of synthesized cholesterol goes through lathosterol, while only 20% goes through desmosterol. Therefore lathosterol is the only valid marker of cholesterol product...	wiki	http://www.bostonheartdiagnostics.com/science_portfolio_cholesterol_balance_test.php

Figure 10 Classification Rules for Lathosterol

Based on these definitions

1) Lathosterol (Cholesterol Production Marker)

- Optimal: <90 µmol x 100/mmol of TC
- Borderline: 90 -160 µmol x 100/mmol of TC
- High > 160 µmol x 100/mmol of TC
- Very High > 7.0 mg/L ****Action Value*** (Not on report, only in plug-in)

Handling Ranges in lookup Tables

We can stored the classification ranges in a databse lookup table like this

classification	name	lower	units	upper
Borderline	Beta-Sitosterol	100.000000	µmol x 100/mmol...	180.000000
Borderline	Campesterol	150.000000	µmol x 100/mmol...	260.000000
Borderline	Cholestanol	140.000000	µmol x 100/mmol...	215.000000
Borderline	Desmosterol	90.000000	µmol x 100/mmol...	120.000000
Borderline	Lathosterol	90.000000	µmol x 100/mmol...	160.000000
High	Beta-Sitosterol	180.000000	µmol x 100/mmol...	9999.000000
High	Campesterol	250.000000	µmol x 100/mmol...	9999.000000
High	Cholestanol	250.000000	µmol x 100/mmol...	9999.000000
High	Desmosterol	120.000000	µmol x 100/mmol...	99999.000000
High	Lathosterol	160.000000	µmol x 100/mmol...	99999.000000
Optimal	Beta-Sitosterol	0.000000	µmol x 100/mmol...	100.000000
Optimal	Campesterol	0.000000	µmol x 100/mmol...	150.000000
Optimal	Cholestanol	0.000000	µmol x 100/mmol...	140.000000
Optimal	Desmosterol	0.000000	µmol x 100/mmol...	90.000000
Optimal	Lathosterol	0.000000	µmol x 100/mmol...	90.000000

Figure 11 Classification Ranges in a Database

But are we sure there are no ambiguities or missing ranges?
Can you see the problem with this table?

Detecting Ambiguous Ranges

	Conditions	1	2	3	4	5	6
a	R1.lower < R2.lower	T	-	T	T	F	F
b	R1.upper <= R2.lower	T	-	F	F	-	-
c	R1.lower >= R2.upper	-	T	T	F	T	F
d	R1.upper > R2.upper	-	T	F	-	F	-
e	R1.classification = R2.classification	F	F	F	F	F	F
f							
	Actions						
	Post Message(s)						
	Overrides						

Rule Messages | Natural Language | History | Properties | Rule Statements

Ref	Post	Alias	Text
	Info	R1	OK: {R1.lower}-{R1.upper} is below {R2.lower}-{R2.upper}
	Info	R1	OK: {R1.lower}-{R1.upper} is above {R2.lower}-{R2.upper}
3:6	Violation	R1	Range Conflict for {R1.name}: {R1.lower}-{R1.upper} ({R1.classification}) overlaps {R2.lower}-{R2.upper} ({R2.classification})

Figure 12 Detecting Ambiguous Tanges

Detecting Missing Ranges

This rule sheet will add missing ranges with a classification of 'UNDEFINED'

	Conditions	1
a	anyRange1->exists(lower>lowerRange.upper,lower<higherRange.lower)	F
b	anyRange2->exists(lower>lowerRange.upper, upper<= higherRange.lower,name<>higherRange.name)	F
c	anyRange3->exists(lower<=lowerRange.upper,upper>=higherRange.lower,name= higherRange.name)	F
d		
	Actions	
	Post Message(s)	
A	LabRanges.new[lower=lowerRange.upper,upper=higherRange.lower,name=lowerRange.name,classification='UNDEFINED',units=lowerRange.units]	✓

Figure 13 Detecting Missing Ranges

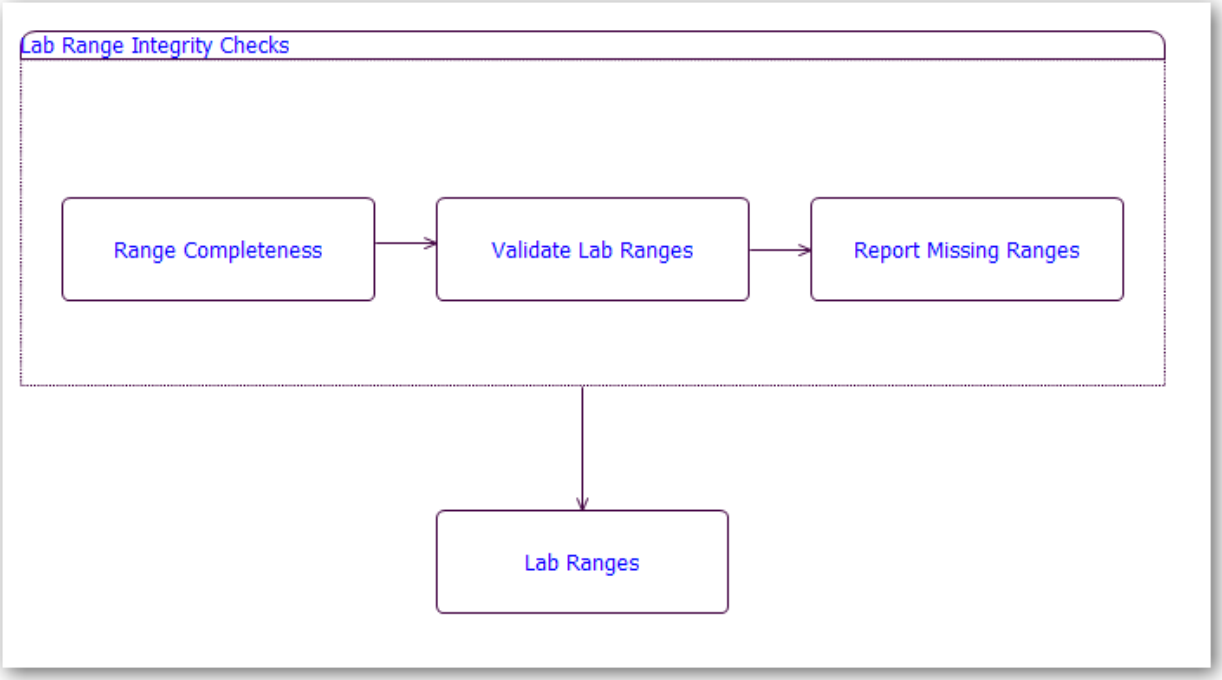
Reporting missing ranges

	Conditions	1
a	LabRanges.classification	'UNDEFINED'
	Actions	
	Post Message(s)	
A		
	Overrides	

Rule Messages | Natural Language | History | Properties

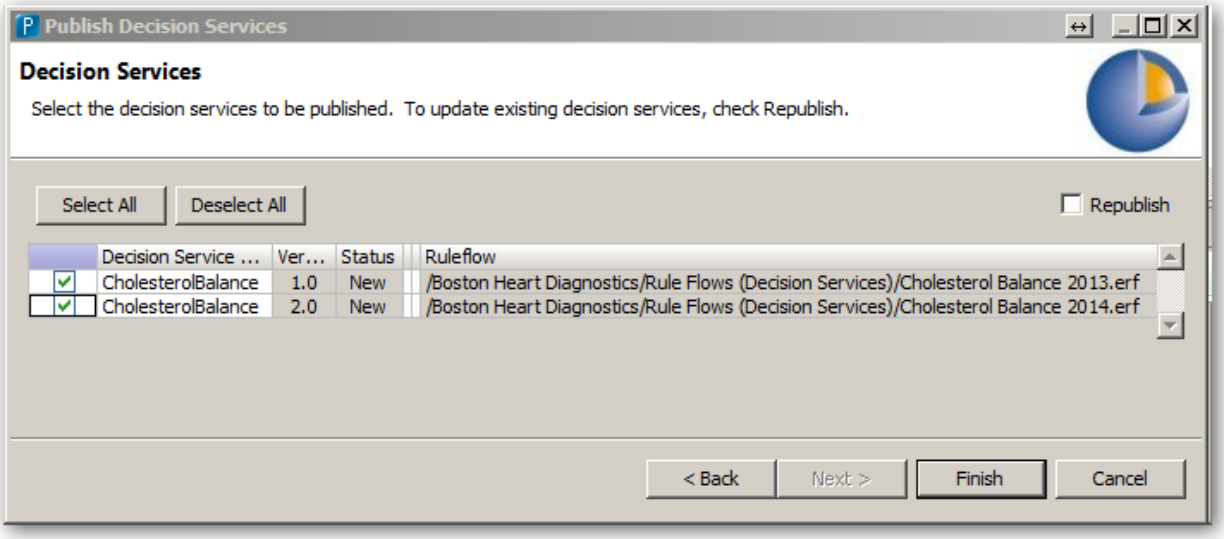
Ref	Post	Alias	Text
1	Violation	LabRanges	Found missing range for {LabRanges.name} {LabRanges.lower}-{LabRanges.upper}

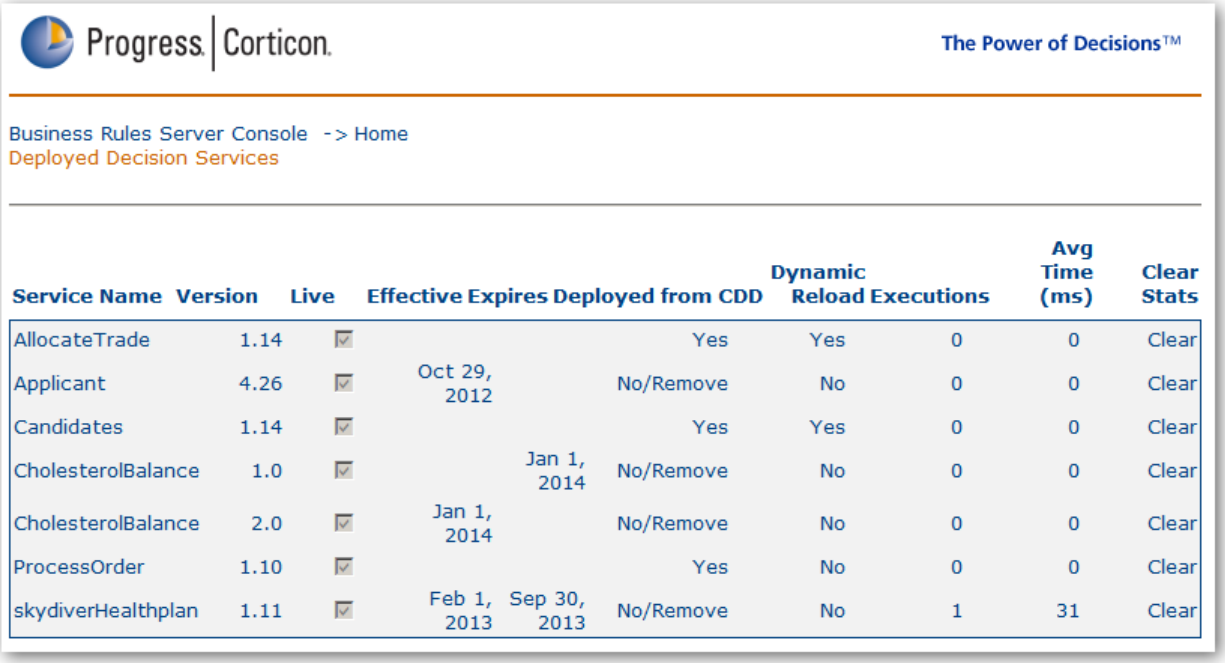
The Range Check Rule Flow



Deployment

Publishing decision services.
Note: Two (slightly) different rule flows (with differing versions and effective dates) but both have the SAME decision service name.
Calling applications only need to supply the name – Corticon will execute the appropriate version automatically.





Service Name	Version	Live	Effective	Expires	Deployed from CDD	Dynamic Reload	Executions	Avg Time (ms)	Clear Stats
AllocateTrade	1.14	☑			Yes	Yes	0	0	Clear
Applicant	4.26	☑	Oct 29, 2012		No/Remove	No	0	0	Clear
Candidates	1.14	☑			Yes	Yes	0	0	Clear
CholesterolBalance	1.0	☑		Jan 1, 2014	No/Remove	No	0	0	Clear
CholesterolBalance	2.0	☑	Jan 1, 2014		No/Remove	No	0	0	Clear
ProcessOrder	1.10	☑			Yes	No	0	0	Clear
skydiverHealthplan	1.11	☑	Feb 1, 2013	Sep 30, 2013	No/Remove	No	1	31	Clear

Appendix – The Business Use Case

A. Starting Instructions

1) Lathosterol (Cholesterol Production Marker)

- Optimal: <90 µmol x 100/mmol of TC
- Borderline: 90 -160 µmol x 100/mmol of TC
- High > 160 µmol x 100/mmol of TC
- Very High > 7.0 mg/L ***Action Value*** (Not on report, only in plug-in)

Data Values Example
System provide the data as follow:

Abbreviation Test Name	ResultCode	Result Value		
Lathosterol	502	140		
Lathosterol	502	>250		
Lathosterol	502	<65		
Lathosterol	502	TNP		Test Not Perform
Lathosterol	502	null		
Lathosterol Absolute	5021	7.4		
• Optimal • Borderline • High • ADL • BDL • TNP • Missing • AVH • AVL • CriticalLow • CriticalHigh • AlertHigh • AlertLow Actual Value >250 <56 44 T/T Absolute Value== Number	Lathosterol Lathosterol Value Lathosterol Absolute	AVH== Action Value High		

2) **Desmosterol (Cholesterol Production Marker)**

- Optimal: < 90 µmol x 100/mmol of TC
- Borderline: 90 – 120 µmol x 100/mmol of TC
- High: > 120 µmol x 100/mmol of TC

- Very High > 5.0 mg/L ***Action Value** (Not on report, only in plug-in)

3) **Beta-sitosterol (Cholesterol Absorption Marker)**

- Optimal: < 100 µmol x 100/mmol of TC
- Borderline: 100 – 180 µmol x 100/mmol of TC
- High: > 180 µmol x 100/mmol of TC

- Very high: > 7.0 mg/L * ***Action Value*** (Not on report, only in plug-in)

4) Campesterol (Cholesterol Absorption Marker)

- Optimal: <150 µmol x 100/mmol of TC
- Borderline: 150 – 260 µmol x 100/mmol of TC
- High: > 260 µmol x 100/mmol of TC

- Very high: > 10.0 mg/L * ***Action Value*** (Not on report, only in plug-in)

5) Cholestanol (Cholesterol Absorption Marker)

- Optimal: < 140 µmol x 100/mmol of TC
- Borderline: 140 – 215 µmol x 100/mmol of TC
- High: > 215 µmol x 100/mmol of TC

- Very high: > 8.0 mg/L * ***Action Value*** (Not on report, only in plug-in)

6) Cholesterol Production/Absorption Balance

- Very Low: < 0.20 ***Action Value*** (Not on report, only in plug-in)

- Low: < 0.5
- Normal: 0.5 - 1.1
- High: > 1.1

- Very High: > 2.1 ***Action Value*** (Not on report, only in plug-in)

B. Interpretations

Plug Ins and Interpretations

1) Borderline Production, Borderline Absorption
   - BORDERLINE cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and statin therapy if LDL-C lowering is indicated.

2) **High Production, Borderline Absorption**
   - HIGH cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and statin therapy if LDL-C lowering is indicated.

3) High Production, High Absorption
   - HIGH cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification, statin and ezetimibe therapy if LDL-C lowering is indicated.

4) High Production, Optimal Absorption
   - HIGH cholesterol production and OPTIMAL absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and statin therapy if LDL-C lowering is indicated.

5) **Borderline Production, High Absorption**
   - BORDERLINE cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification, statin and ezetimibe therapy if LDL-C lowering is indicated.

6) Optimal Production, Borderline Absorption
   - OPTIMAL cholesterol production and BORDERLINE absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and ezetimibe therapy if LDL-C lowering is indicated.

7) Optimal Production, High Absorption
   - OPTIMAL cholesterol production and HIGH absorption may be associated with elevated LDL-C levels and increased heart disease risk.
   - Lifestyle modification and ezetimibe therapy if LDL-C lowering is indicated.

8) Optimal Production, Optimal Absorption
- OPTIMAL cholesterol production and OPTIMAL absorption.
-(no treatment considerations)

9) Borderline Production, Optimal Absorption
-BORDERLINE cholesterol production and OPTIMAL absorption may be associated with elevated LDL-C levels and increased heart disease risk.
-Lifestyle modification and statin therapy if LDL-C lowering is indicated.

Additional statements to appear along with interpretations selected from 1-9 above:

10) Very High Lathosterol (Action Value)
Lathosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol production.

11) Very High Desmosterol (Action Value)
Desmosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol production..

12) Very High Beta-Sitosterol and Campesterol (Action Value)
Beta-sitosterol level is very HIGH at [_] mg/L. Campesterol level is very HIGH at [_] mg/L. Very high absolute cholesterol absorption values may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia and increased heart disease risk.

13) Very High Beta-sitosterol (Action Value)*
Beta-sitosterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia, and increased heart disease risk.

14) Very High Campesterol (Action Value)*
Campesterol level is very HIGH at [__]mg/L, consistent with markedly increased cholesterol absorption and may be associated with elevated LDL-C levels, tendon xanthomas, phytosterolemia, and increased heart disease risk.

15) Very High Cholestanol (Action Value)
Cholestanol level is very HIGH at [__]mg/L, and may be associated with tendon xanthomas, neurological disease, and cerebrotendinous xanthomatosis.

16) Lathosterol below detection limit*
Lathosterol level is BELOW detection limit, indicating DECREASED cholesterol production.

17) Desmosterol below detection limit*
Desmosterol level is BELOW detection limit.

18) Beta-sitosterol below detection limit*

Beta-sitosterol level is BELOW detection limit, indicating DECREASED cholesterol absorption.

19) Campesterol below detection limit*
Campesterol level is BELOW detection limit, indicating DECREASED cholesterol absorption.

20) Very High Cholesterol Production/Absorption Balance (Action Value)
Cholesterol Balance Score is very HIGH at [__], consistent with markedly increased cholesterol production.

21) Very Low Cholesterol Production Absorption Balance (Action Value)
Cholesterol Balance Score is very low at [__], consistent with markedly increased cholesterol absorption.

22) Current: If any results are null* (requires revision – see Exception Handling #2 below)
Cholesterol Balance score could not be calculated due to technical limits of the assay.

C. Classifications/Grouping

A. Note for programming with regard to production: always use the normalized lathosterol to categorize people as optimal, borderline, or high, even if there is an alert value on desmosterol (reason: 80% of the production goes through lathosterol).

B. With regard to absorption use only normalized beta-sitosterol and normalized campesterol, even if there an alert value very high cholestanol, for normalized beta-sitosterol and campesterol, the higher value supercedes the lower value:
   1) if the absorption markers are borderline/borderline, the call is borderline
   2) if the absorption markers are borderline/low, the call is borderline
   3) if the absorption markers are borderline/high, the call is high
   4) if the absorption markers are optimal/borderline, the call is borderline
   5) if the absorption markers are optimal/optimal, the call is optimal
   6) if the absorption markers are optimal/high, the call is high
   7) if the absorption markers are high/high, the call is high
   8) if the absorption markers are high/borderline, the call is high
   9) if the absorption markers are high/optimal, the call is high

C. For Action Values please put the actual value in absolute terms as mg/L in the plug ins (applies for plug ins 10 – 15 above).

D. Exception Handling

1. If desmosterol is at different category level (optimal, borderline or high) than lathosterol: insert statement: “Desmosterol accounts for 20% of production.”

2. If any value is missing (usually desmosterol for older patient reports), XXXXXXXXXXX (currently not possible with Boolean structure – current Interpretation #22)
3. If LDL-C level is very high (>XX), the normalized values will show one category: optimal, borderline, high; while the absolute values may be very high, in the reportable range. In the event of discordance, insert comment: "Normalized values are skewed by extremely high LDL-C levels."
4. Values below BDL or ADL – insert BDL or ADL limit value to calculate cholesterol balance score.