

Elecsys Vitamin B12 II

REF			SYSTEM
07028121190*	07028121500	300	cobas e 402
07028121214*			cobas e 801

* Some kits shown may not be available in all countries.

English

System information

Short name	ACN (application code number)
B12 2	10088

Intended use

Binding assay for the in vitro quantitative determination of vitamin B12 in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Vitamin B12 measurements, performed with this assay in human serum and plasma, are used as an aid in diagnosis of vitamin B12 deficiency, an underlying cause of clinical conditions such as megaloblastic anemia and central nervous system (CNS) disorders (e.g. peripheral neuropathy, dementia, poor cognitive performance, depression).

Vitamin B12, also referred to as cobalamin, is a complex organometallic compound in which a cobalt atom is situated within a corrin ring. It is a water-soluble vitamin which is synthesized by microorganisms. It cannot be synthesized in the human body and is seldom found in products of plant origin. Main sources of vitamin B12 are meat, fish, eggs and dairy products.¹ The uptake from the intestine into the circulation is a complex mechanism depending on vitamin B12-binding molecules, receptors, and transporters. In the stomach, the free vitamin B12 molecule is bound to haptocorrin (R protein) and travels with it into the duodenum, where the haptocorrin is digested. Liberated vitamin B12 then binds to intrinsic factor (IF), a glycoprotein that is produced by the gastric parietal cells. When the vitamin B12-IF complex reaches the distal ileum, it is bound by specific receptors known as the "cubam complex", on the surface of mucosal epithelial cells and it is internalized.¹ In circulation, vitamin B12 then binds to two circulating binding proteins, haptocorrin (HC) and transcobalamin (TC); only the TC-bound fraction is the bioactive fraction, transporting vitamin B12 to receptors on cell membranes throughout the body for cellular uptake.¹

Vitamin B12 is the cofactor for two enzymes, methionine synthase and methylmalonyl CoA mutase.^{2,3} Methionine synthase, located in the cytoplasm, requires vitamin B12 in the form of methylcobalamin and catalyzes the conversion of homocysteine to methionine, an essential amino acid. During this step a methyl group is transferred from methyltetrahydrofolate to the amino acid.³ This enzyme links the methylation pathway through synthesis of the methyl donor S-adenosyl methionine and the pathway in which purine and pyrimidine are synthesized via generation of tetrahydrofolate.³ In the form of 5'-deoxyadenosylcobalamin, vitamin B12 is also required for the mitochondrial enzyme methylmalonyl CoA mutase, which converts methylmalonyl CoA to succinyl CoA. This is a step in the oxidation of odd-chain fatty acids and catabolism of ketogenic amino acids.³ Thus, vitamin B12 is important for DNA synthesis, regenerating methionine for protein synthesis and methylation, as well as for the development and initial myelination of the CNS and for the maintenance of normal CNS function.^{2,3}

Vitamin B12 deficiencies are common in wealthier countries principally among the elderly, yet are most prevalent in economically disadvantaged populations. In general the prevalence increases with age.^{4,5}

The most frequent cause of severe vitamin B12 deficiency is a lack of intrinsic factor due to autoimmune atrophic gastritis. The disease is historically called "pernicious anemia", even though many patients present with mainly neurologic manifestations. Examples of other causes for vitamin B12 deficiency are malabsorption due to gastrectomy, inflammatory bowel disease or dietary deficiency, e.g. in strict vegetarians or vegans.²

Vitamin B12 deficiency impacts red blood cell synthesis, resulting in megaloblastic anemia due to abnormal DNA synthesis.³ In addition, severe vitamin B12 deficiency can result in demyelination of nerves, which may lead to peripheral neuropathy, dementia, poor cognitive performance, and depression.³ Other effects of vitamin B12 deficiency or depletion are

increased risk of neural tube defects, osteoporosis, cerebrovascular and cardiovascular diseases.³ Early diagnosis is essential, because of the latent nature of this disorder and the risk of permanent neurological damage.^{3,5}

Generally, the primary test performed to confirm the diagnosis of vitamin B12 deficiency is measurement of the serum vitamin B12 level.² Recent publications suggest that in addition the following biomarkers should be measured to improve the specificity of diagnosis: folate, methylmalonic acid (MMA), homocysteine and holotranscobalamin.^{2,5,6,7}

The Elecsys Vitamin B12 II assay employs a competitive test principle using intrinsic factor specific for vitamin B12. Vitamin B12 in the sample competes with the added vitamin B12 labeled with biotin for the binding sites on the ruthenium labeled intrinsic factor complex^{a)}.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Test principle

Competition principle. Total duration of assay: 27 minutes.

- 1st incubation: By incubating the sample (9 µL) with the vitamin B12 pretreatment 1 and pretreatment 2, bound vitamin B12 is released.
- 2nd incubation: By incubating the pretreated sample with the ruthenium-labeled intrinsic factor, a vitamin B12-binding protein complex is formed, the amount of which is dependent upon the analyte concentration in the sample.
- 3rd incubation: After addition of streptavidin-coated microparticles and vitamin B12 labeled with biotin, the still-vacant sites of the ruthenium-labeled intrinsic factor become occupied, with formation of a ruthenium-labeled intrinsic factor vitamin B12 biotin complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

Reagents - working solutions

The **cobas e** pack (M, R1, R2) and the pretreatment reagents (PT1, PT2) are labeled as B12 2.

PT1 Pretreatment reagent 1, 1 bottle, 7.3 mL:
Dithiothreitol 1.028 g/L; stabilizer, pH 5.5.

PT2 Pretreatment reagent 2, 1 bottle, 6.3 mL:
Sodium hydroxide 40 g/L; sodium cyanide 2.205 g/L.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Intrinsic factor-Ru(bpy)₃²⁺, 1 bottle, 18.8 mL:
Ruthenium labeled recombinant porcine intrinsic factor 4 µg/L;
cobinamide dicyanide 15 µg/L; stabilizer; human serum albumin;
phosphate buffer, pH 5.5; preservative.

R2 Vitamin B12-biotin, 1 bottle, 15.8 mL:
Biotinylated vitamin B12 25 µg/L; biotin 3 µg/L; phosphate buffer,
pH 7.0; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:

Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

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Environmental hazards:

Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:



Danger

H290	May be corrosive to metals.
H301	Toxic if swallowed.
H314	Causes severe skin burns and eye damage.
H317	May cause an allergic skin reaction.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing mist or vapours.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.

Response:

P301 + P310 + P330	IF SWALLOWED: Immediately call a POISON CENTER/ doctor. Rinse mouth.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water.
P304 + P340 + P310	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/ doctor.
P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.^{8,9}

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:

unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Na-heparin, Li-heparin, K₂-EDTA and K₃-EDTA plasma.

Li-heparin plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within $\pm 2 \times$ Limit of Blank + coefficient of correlation ≥ 0.95 .

Stable for 2 hours at 15-25 °C, 48 hours at 2-8 °C, 56 days at -20 °C (± 5 °C). Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Vitamin B12 determinations should be performed on serum or plasma samples from fasting patients.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- [REF] 07212780190, Vitamin B12 II CalSet, for 4 x 1.0 mL
 - [REF] 05618860190, PreciControl Varia, for 4 x 3.0 mL
 - [REF] 07299001190, Diluent Universal, 36 mL sample diluent
 - General laboratory equipment
 - **cobas e** analyzer
- Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:
- [REF] 06908799190, ProCell II M, 2 x 2 L system solution
 - [REF] 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
 - [REF] 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
 - [REF] 06908853190, PreClean II M, 2 x 2 L wash solution
 - [REF] 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
 - [REF] 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
 - [REF] 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
 - [REF] 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

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Calibration

Traceability: This method has been standardized against the Elecsys Vitamin B12 assay ([REF] 04745736190).

Accuracy to WHO Standard 03/178: A study was performed to evaluate the accuracy of the Elecsys Vitamin B12 II assay using the Vitamin B12 World Health Organization International Standard 03/178.¹⁰ Two reagent lots were used on 16 instruments. The mean recovery of the target value of WHO IS 03/178 (480 pg/mL) was 102 %.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use Elecsys PreciControl Varia or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in pmol/L or pg/mL).

Conversion factors: $\text{pmol/L} \times 1.36 = \text{pg/mL}$
 $\text{pg/mL} \times 0.738 = \text{pmol/L}$

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	$\leq 1112 \mu\text{mol/L}$ or $\leq 65 \text{ mg/dL}$
Hemoglobin	$\leq 0.621 \text{ mmol/L}$ or $\leq 1000 \text{ mg/dL}$
Intralipid	$\leq 1500 \text{ mg/dL}$
Biotin	$\leq 205 \text{ nmol/L}$ or $\leq 50 \text{ ng/mL}$
Rheumatoid factors	$\leq 1500 \text{ IU/mL}$
IgG	$\leq 2.8 \text{ g/dL}$
IgA	$\leq 1.6 \text{ g/dL}$
IgM	$\leq 1 \text{ g/dL}$

Criterion: For concentrations of 100-200 pg/mL the deviation is $\leq 20 \text{ pg/mL}$. For concentrations $> 200 \text{ pg/mL}$ the deviation is $\leq 10 \text{ %}$.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. $> 5 \text{ mg/day}$) until at least 8 hours following the last biotin administration.

Because intrinsic factor is typically used as the binding protein in serum vitamin B12 assays, anti-intrinsic factor antibodies (which are common in pernicious anemia) can lead to elevated vitamin B12 measurement

values.^{11,12,13} The Elecsys Vitamin B12 II assay is designed to avoid interference due to anti-intrinsic factor antibodies.¹⁴

Pharmaceutical substances

In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

Samples with extremely high total protein concentrations (hyperproteinemia) are not suitable for use in this assay. Hyperproteinemia may be caused by, but not limited to, the following conditions: Lymphoma^{15,16}, bone marrow disorders such as multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), Waldenström macroglobulinemia, plasmocytoma^{15,16,17,18,19,20,21}, Amyloidosis^{21,22}. Respective samples may lead to the formation of protein gel in the assay cup, which may cause a run abort. The critical total protein concentration is dependent upon the individual sample composition.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Note: The presence of immunoglobulin-vitamin B12 complexes may cause unexpectedly high values of vitamin B12.^{23,24}

Limits and ranges

Measuring range

100-2000 pg/mL or 73.8-1476 pmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as $< 100 \text{ pg/mL}$ or $< 73.8 \text{ pmol/L}$. Values above the measuring range are reported as $> 2000 \text{ pg/mL}$ or $> 1476 \text{ pmol/L}$ (or up to 4000 pg/mL or 2952 pmol/L for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 50 pg/mL (36.9 pmol/L)

Limit of Detection = 100 pg/mL (73.8 pmol/L)

Limit of Quantitation = 150 pg/mL (111 pmol/L)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from $n \geq 60$ measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of $\leq 20 \text{ %}$.

It has been determined using low concentration vitamin B12 samples.

Dilution

Samples with vitamin B12 concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the analyzer or manually). The concentration of the diluted sample must be $\geq 1000 \text{ pg/mL}$ or $\geq 738 \text{ pmol/L}$.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzer, the software automatically takes the dilution into account when calculating the sample concentration.

Note: Sample-dependent non-linearity upon dilution is seen with samples having analyte levels beyond the measuring range. As Diluent Universal may contain low levels of endogenous vitamin B12, it is recommended that linearity studies be performed using a known low analyte-containing serum pool. Samples outside the measuring range can be diluted 1:2 with Diluent Universal; the effect of endogenous vitamin B12 concentration is insignificant at these levels.

Expected values

Because differences may exist with respect to population and dietary status, it is recommended that normal ranges be determined by each

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laboratory over a suitable period of time and in a statistically significant number of samples before clinical significance is attached to the results.

The values shown below were performed on samples from an apparently healthy population, using the Elecsys Vitamin B12 II assay. The calculation is based on 135 sera (68 men, 67 women). The age range was between 20 and 78 years. Pregnant women were excluded. The reference population was selected according to normal homocysteine values.

N	Median		Range (2.5 th -97.5 th percentile)	
	pg/mL	pmol/L	pg/mL	pmol/L
135	425	314	197-771	145-569

These values should only be used as guidance.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and cobas e 801 analyzers					
Sample	Mean pg/mL	Repeatability		Intermediate precision	
		SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	131	9.45	7.2	10.6	8.1
Human serum 2	168	8.50	5.1	9.74	5.8
Human serum 3	206	7.92	3.9	9.28	4.5
Human serum 4	999	11.8	1.2	18.3	1.8
Human serum 5	1984	22.4	1.1	47.4	2.4
PreciControl Varia1	462	10.6	2.3	11.9	2.6
PreciControl Varia2	901	14.2	1.6	20.4	2.3

cobas e 402 and cobas e 801 analyzers					
Sample	Mean pmol/L	Repeatability		Intermediate precision	
		SD pmol/L	CV %	SD pmol/L	CV %
Human serum 1	96.7	6.97	7.2	7.82	8.1
Human serum 2	124	6.27	5.1	7.19	5.8
Human serum 3	152	5.84	3.9	6.85	4.5
Human serum 4	737	8.71	1.2	13.5	1.8
Human serum 5	1464	16.5	1.1	35.0	2.4
PreciControl Varia1	341	7.82	2.3	8.78	2.6
PreciControl Varia2	665	10.5	1.6	15.1	2.3

Method comparison

a) A comparison of the Elecsys Vitamin B12 II assay, [REF] 07212771190 (y) with the Elecsys Vitamin B12 assay (x) using clinical samples gave the following correlations (pg/mL):

Number of samples measured: 100

Passing/Bablok ²⁵	Linear regression
$y = 0.952x + 15.1$	$y = 0.957x + 11.6$
$\tau = 0.977$	$r = 0.999$

The sample concentrations were between 69 and 1890 pg/mL (51 and 1395 pmol/L).

b) A comparison of the Elecsys Vitamin B12 II assay, [REF] 07028121190 (cobas e 801 analyzer; y), with the Elecsys Vitamin B12 II assay, [REF] 07212771190 (cobas e 601 analyzer; x), gave the following correlations (pg/mL):

Number of serum samples measured: 127

Passing/Bablok ²⁵	Linear regression
$y = 1.01x + 0.004$	$y = 1.05x - 20.4$
$\tau = 0.977$	$r = 0.998$

The sample concentrations were between 113 and 1833 pg/mL (83.4 and 1353 pmol/L).

c) A comparison of the Elecsys Vitamin B12 II assay, [REF] 07028121190 (cobas e 402 analyzer; y), with the Elecsys Vitamin B12 II assay, [REF] 07028121190 (cobas e 801 analyzer; x), gave the following correlations (pg/mL):

Number of serum samples measured: 143

Passing/Bablok ²⁵	Linear regression
$y = 0.989x + 10.7$	$y = 0.987x + 12.5$
$\tau = 0.968$	$r = 0.999$

The sample concentrations were between 116 and 1861 pg/mL (85.6 and 1373 pmol/L).

Analytical specificity

The following cross-reactivities were found, tested with vitamin B12 concentrations of 193 pg/mL and 1196 pg/mL.

Cross-reactant	Maximum concentration tested ng/mL	Cross-reactivity %
Cobinamide dicyanide	210	0.0

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Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

+800 5505 6606



For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume for reconstitution
	Global Trade Item Number

Rx only For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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Additions, deletions or changes are indicated by a change bar in the margin.

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